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CASE REPORT

Nonfatal and fatal intoxications with pure caffeine – report of three different cases

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Abstract Caffeine is not usually perceived as a drug by most people because it is found in many foods and drinks, including caffeinated energy drinks, as well as in over the counter analgesics and cold preparations. Recently in Poland it has become increasingly common to take pure caffeine, bought through online stores, as a psychoanaleptic. This creates a much higher risk of severe and even fatal poisoning in comparison with the risk associated with the abuse of food products and non-prescription medicines containing low doses of caffeine. This paper presents three different cases of poisoning that occurred when pure caffeine was taken as psychostimulant; in cases 1 and 2 poisoning was the result of a single overdose, while in the case 3 poisoning resulted from a cumulative overdose. In the case 1 there was a severe intoxication (persistent vomiting, hypotension, tremor), and the concentration of caffeine in the blood was found to be 80.16 μg/mL. The patient was treated using hemodialysis, which caused a rapid decrease in blood levels of caffeine and relief of the clinical symptoms of poisoning. Cases 2 and 3 were fatal poisonings, and recorded levels of caffeine in post mortem blood samples were 140.64 μg/mL and 613.0 μg/mL. In case 2 the patient died 10 min after admission to hospital as a result of sudden cardiac arrest, which was preceded by an attack of convulsions, and in case 3 death occurred in home and was also sudden in nature. Taking pure caffeine as a stimulant is associated with a high risk of overdose and the development of serious and even fatal poisoning, and those using pure caffeine are generally completely unaware of these risks. In such cases, death is usually sudden due to functional mechanisms.

Keywords Pure caffeine · Nonfatal intoxication · Fatal intoxication · Hemodialysis

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Introduction

Caffeine, a naturally occurring purine alkaloid found in the leaves, seeds, or fruits of a number of plants, is the most widely used central nervous system stimulant in the world. Caffeine is not usually perceived as a drug by most people because it is found in many foods and drinks, including caffeinated energy drinks, as well as in over-the-counter analgesics and cold preparations [1, 2]. Food, drinks, and over-the-counter drugs usually contain low doses of caffeine, e.g. tea, 30-50 mg/cup; coffee, 70-150 mg/cup; cola drinks 35-55 mg/360 ml; chocolate bars 6-25 mg/bar; cold preparations 30-75 mg; chocolate 70-198 mg/100 g [2, 3]. The estimated lethal dose of caffeine in an untreated adult is 5-10 g [4, 5]; one tablespoon of pure caffeine contains approximately 15 g. Recently in Poland it has become increasingly common to ingest pure caffeine, purchased from online stores, as a psychoanaleptic. This creates a much greater risk of severe and even fatal poisoning compared with the abuse of food products and non-prescription medicines containing low

doses of caffeine. Those who take pure caffeine are generally completely unaware of the risk of fatal poisoning.

This paper presents three different cases of poisoning with pure caffeine taken as a psychostimulant; the first was treated effectively with the use of hemodialysis, whereas the second and third proved fatal. The poisonings in cases 1 and 2 were the result of a single overdose, while the poisoning in case 3 was the result of a cumulative overdose.

Case presentation

Case 1

A 36-year-old male professional driver with no significant medical history ingested, in the course of a single evening, 2 heaped tablespoons of caffeine (approximately 30 g), which had been purchased from an online store in the form of one-pound packages of caffeine anhydrous powder. He had ingested the caffeine for its analeptic action as he wished to prevent drowsiness during prolonged driving at night.

An hour after ingesting the caffeine, he experienced agitation, abdominal pain, and extremely severe nausea; severe vomiting, initially with food and bile content, ensued. The patient also produced several loose stools. Due to the severe vomiting, the patient was unable to leave his house; he lay in bed all night, vomiting profusely. In the morning he called an ambulance, which transported him to the hospital.

At the time of his admission to the Department of Toxicology, the patient was agitated but with preserved logical verbal contact. He complained of abdominal pain, severe nausea and abundant vomiting. Features of dehydration (dry mucous membranes, standing skin folds), arterial hypotension (75/30 mmHg), sinus tachycardia (110/min) with extremely frequent supraventricular extrasystoles, and muscle tremors and fasciculations were noted. In laboratory studies, leukocytosis (21.56G/L), hyperglycemia (172 mg%), hypokalemia (2.9 mmol/L), elevated nitrogen metabolite levels (urea, 65.8 mg%; creatinine, 1.65 mg%), an elevated creatine phosphokinase level (CPK) (8885 U/L; normal range is 39-308 U/L), and mild alkalosis (pH 7.47; BE 3.7 mmol/L) drew the attention of clinicians. The caffeine concentration in his blood serum was determined by GC-MS/MS as 80.16 μg/mL.

Immediately following admission, the patient received an intravenous antiemetic (ondansetron), a proton pump inhibitor (pantoprazole), a sedative (diazepam), and infusion liquids (crystalloids containing potassium chloride), which reduced the frequency of vomiting and muscle fasciculations, induced regression of psychomotor agitation, and raised the patient's blood pressure to 95/45 mmHg.

A 6-h hemodialysis treatment was also started. After 4 h of hemodialysis, the plasma caffeine levels had dropped to 16.87 μg/mL, and by the end of the 6 h this had fallen to 3.82 μg/mL. This was accompanied by complete relief of clinical signs of intoxication and normalization of serum concentrations of nitrogen metabolites, potassium and glucose, and gasometric parameters.

Over the next three days of hospitalization, normalization of the white blood cell count and CPK level was observed. The patient was discharged in a good general condition.

Case 2

A 27-year-old man with no significant medical history, but who was prone to abusing caffeine, ingested after a workout at a gym ("to strengthen himself"), three tablespoons (approximately 45 g) of pure caffeine purchased from an online store in the form of caffeine anhydrous powder. About an hour after ingesting the caffeine, nausea and multiple instances of vomiting ensued. After several hours of discomfort and heavy vomiting, the patient reported to the emergency room.

On admission to the hospital, the patient was awake, agitated, and alluded logical verbal contact. He complained of extremely severe nausea, vomiting with serous content, severe muscle tremors, and sinus tachycardia up to 150beats/min. His blood pressure was measured at 120/70 mmHg. About 10 min after his admission to hospital, he suffered generalized seizures, after which sudden cardiac arrest occurred due to electromechanical dissociation and asystole. Cardiopulmonary resuscitation was initiated immediately and carried out for 50 min, but without any clinical effect.

Additional laboratory tests on blood taken prior to cardiac arrest yielded the following results: CPK level, 787 U/l [normal up to 195]; CK-MB, 62.7 U/l [normal up to 25]; troponin T, 14.7 pg/ml [normal up to 14]; creatinine, 1.64 mg/dl; eGFR, 54 [normal >60]; glucose, 183 mg%; potassium, 2.9 mmol/L.

Post-mortem examinations showed significant edema of the lungs and brain, steatosis, liquidity and stagnation of blood in the internal organs, congestion and small hemorrhages in the myocardium with the presence of fuchsin-stained cardiomyocyte areas (positive Selye staining), and lymphocytic inflammatory infiltrations in the liver, esophagus, and intestines. In the biological material collected during the autopsy, the presence of caffeine, in a concentration of 140.64 μg/mL (blood) and 36.48 μg/mL (urine), was confirmed using the ELISA and HPLC-MS methods.

Case 3

A 20-year-old woman was found dead on the floor of her room by her mother. The woman's body was contaminated with vomit. According to a relative, the woman had not been seriously ill, and was not taking prescription medicines. Due to an imminent secondary school certificate exam she had been studying a great deal, especially at night, at which time she repeatedly drank energy drinks that she had prepared

herself. Information obtained from the prosecutor indicated that the woman had ordered pure caffeine via the internet about two weeks prior to her death. During the examination of the deceased's room, a container containing a white, crystalline substance described as caffeine was found in a cupboard. Traces of a similar substance were found in a cup belonging to the deceased. Physicochemical tests showed that both the container and the cup contained pure caffeine.

Post-mortem examination of the victim's body revealed no external injuries. No major significant pathological lesions were found, only minor simple kidney cysts and bronchitis. The autopsy revealed the presence of the characteristics of sudden death in the form of abundant *livores mortis*, blood liquidity, congestion of the internal organs, and features of acute cardiopulmonary failure such as edema of the brain and lungs.

Toxicological tests of biological material collected during autopsy using the GC-MS/MS method revealed the presence of caffeine at a concentration of 613.0 μg/mL (blood) and 218.0 mg μg/mL (urine).

Discussion

The pharmacological action of caffeine results from three main mechanisms: adenosine receptor antagonism, increases in the level of cAMP through inhibition of phosphodiesterase, and an enhanced intracellular calcium level. The result of these three mechanisms of action is a variety of clinical signs of acute toxicity: nausea, vomiting, diarrhea, hyper- or hypotension, tachycardia, arrhythmia, insomnia, agitation, delirium, psychosis, muscle fasciculations, seizures, rhabdomyolysis, and laboratory abnormalities such as hypokalemia, hyperglycemia, leukocytosis, and myoglobinuria [1, 2, 6–8].

In the first and second cases, the patients ingested potentially lethal single doses of caffeine (approximately 30 and 45 g, respectively). As a result, one hour after ingestion, severe signs of toxicity developed. The early development of symptoms of poisoning was associated with the rapid absorption of caffeine from the gastrointestinal tract. Caffeine peak serum concentration is reached after 1–1.5 h [2].

In the first case, at the time of the patient's admission to the Department of Toxicology, the concentration of caffeine in the blood was 80.16 μg/mL; in the second case, toxicological studies were performed post mortem, and the concentration of caffeine in the blood was determined at 140 μg/mL. A particularly high level of caffeine in the blood was found in the autopsy material in the third case (613.0 μg/mL). It should be noted, however, that in all of the presented cases, the concentration of caffeine in the blood reached a value considered fatal (about 80 μg/mL) [2]. The particularly high blood concentration of caffeine in the third case can be explained by a route of caffeine administration different from that in the other cases. In this case poisoning was not, in fact, the result of ingestion of a single lethal dose of caffeine, but cumulative in nature due to multiple repeated doses. We must remember that in children and young people, the biological half-life of caffeine is as high as 14.4 h, much longer than in adults (3–7.5 h) [9], which favors the accumulation of caffeine, especially in the case of multiple repeated doses. The research of Aranda et al. showed that the adult plasma clearance rate of caffeine was achieved at 3 to 4½ months of age. Plasma half-life and elimination rate reached adult levels after 3 to 4½ months and appeared to exceed adult capacity thereafter [10].

The antagonist effect of caffeine on the adenosine receptors can cause vasoconstriction and an increase in blood pressure in the course of intoxication. However, in the first of the cases, arterial hypotension was observed, most likely caused by significant dehydration as a result of persistent and prolonged vomiting. In the first two cases, significant hypokalemia was also observed. This is a common symptom of caffeine poisoning because caffeine, through stimulating Na^+/K^+-ATPase, directly lowers serum potassium, and increases the risk of loss of this ion due to vomiting and increased diuresis. Hypokalemia can in turn exacerbate the risk of arrhythmia induced by caffeine [11, 12]. Therefore, in cases of caffeine poisoning, rapid supplementation of hydroelectrolyte deficiencies, especially of potassium, is very important. Symptomatic treatment helps to stabilize the patient's clinical status and enables initiation of extracorporeal drug elimination from the blood. In the first case, symptomatic treatment resulted in increased blood pressure, alleviation of nausea and vomiting, reduction of intensity of muscle tremors, and the resolution of psychomotor agitation. It appears that the use of antagonists of the serotonin receptor, such as ondansetron, should be the treatment of choice to combat the symptoms of nausea and vomiting in the course of caffeine poisoning, since, unlike metoclopramide, these drugs do not stimulate the motility of the gastrointestinal tract, which in caffeine poisoning is generally increased. In the first and second cases, severe muscle tremor, associated with an increase in creatine phosphokinase serum levels, was observed. These symptoms were related to a caffeine-induced increase in intracellular calcium concentrations in muscle cells [13]. Benzodiazepines, which additionally reduce the risk of seizures and exert a pronounced sedative effect, are effective drugs in such cases.

In the first case, due to severe symptoms of poisoning, physicians decided to institute hemodialysis. This procedure resulted in a rapid decrease in the concentration of caffeine in the patient's blood, which was accompanied by

rapid relief of the clinical symptoms of poisoning. The pharmaco- and toxicokinetic properties of caffeine (distribution volume, 0.5–0.7 L/kg; protein binding, 17%) enable the substance to be removed by means of hemodialysis or charcoal hemoperfusion [1, 2]; therefore these methods should be used in severe, potentially fatal cases of caffeine poisoning [1, 2, 14, 15]. In the second case, sudden cardiac arrest occurred almost immediately after admission of the patient to the hospital, and thus the use of extracorporeal elimination of caffeine from the patient's blood was impossible, despite the existence of indications for this procedure.

Death in the case of caffeine poisoning is usually sudden in nature, and usually caused by arrhythmia and/or apnea following convulsions and seizures [6, 16, 17], as confirmed by our clinical observations and the results of post-mortem examinations.

Conclusions

Ingesting pure caffeine as a stimulant is associated with a high risk of overdose and the development of serious, even fatal, poisoning. In such cases, death is usually sudden, due to functional mechanisms. It appears that there is a need to introduce legislation controlling the purchase of pure caffeine by private individuals, as well as a need for a media campaign highlighting the risks of uncontrolled use of this substance in its pure form.

Key points

1. Caffeine is widely regarded as a safe stimulant.
2. This paper presents three different cases of poisoning due to pure caffeine taken as a psychostimulant.
3. Death following caffeine ingestion is usually sudden, due to functional mechanisms.
4. The concentrations of caffeine in blood in our cases ranged from 80.16 to 613.0 μg/mL.

Compliance with ethical standards The authors declare that they have no conflicts of interest.

For this type of study, formal consent is not required.

References

1. Engebretsen KM, Harris CR. Caffeine and related nonprescription sympathomimetics. In: Ford MD, Delaney KA, Ling LJ, Erickson WB, editors. Clinical toxicology. Philadelphia: Saunders Company; 2001. p. 310–5.
2. Leikin JB, Paloucek FP. Poisoning & toxicology handbook. Hudson: Lexi-Comp Inc.; 2002. p. 311–2.
3. Musgrave IF, Farrington R, Hoban C, Byard RW. Caffeine toxicity in forensic practice: possible effects and under-appreciated sources. Forensic Sci Med Pathol. 2016;12:299–303.
4. Curatolo PW, Robertson D. The health consequences of caffeine. Ann Intern Med. 1983;98:641–53.
5. Mack RB. A tasteless proposal: Caffeine overdose. Am J Med. 1990;89:368.
6. Jabbar SB, Hanly MG. Fatal caffeine overdose: a case report and review of literature. Am J Forensic Med Pathol. 2013;34:321–4.
7. Rudolph T, Knudsen K. A case of fatal caffeine poisoning. Acta Anaesthesiol Scand. 2010;54:521–3.
8. Campana C, Griffin PL, Simon EL. Caffeine overdose resulting in severe rhabdomyolysis and acute renal failure. Am J Emerg Med. 2014;32(111):e3–4.
9. Kanfer I, Dowse R. Vuma V pharmacokinetics of oral decongestants. Pharmacotherapy. 1993;13:116S–28S.
10. Aranda JV, Collinge JM, Zinman R, Watters G. Maturation of caffeine elimination in infancy. Arch Dis Child. 1979;54:946–9.
11. Passmore AP, Kondowe GB, Johnston GD. Renal and cardiovascular effects of caffeine: a dose-response study. Clin Sci. 1987;72:749–56.
12. Rudy D, Lee S. Coffee and hypokalemia. J Fam Pract. 1988;26:679–80.
13. Snyder SH, Skylar P. Behavioral and molecular action of caffeine: focus on adenosine. J Psychiatr Res. 1984;18:91–106.
14. Ishigaki S, Fukasawa H, Kinoshita-Katahashi N, Yasuda H, Kumagai H, Furuya R. Caffeine intoxication successfully treated by hemoperfusion and hemodialysis. Intern Med. 2014;53:2745–7.
15. Holstege CP, Hunter Y, Baer AB, Savory J, Bruns DE, Boyd JC. Massive caffeine overdose requiring vasopressin infusion and hemodialysis. J Toxicol Clin Toxicol. 2003;41:1003–7.
16. Banerjee P, Ali Z, Levine B, Fowler DR. Fatal caffeine intoxication: a series of eight cases from 1999 to 2009. J Forensic Sci. 2014;59:865–8.
17. Yamamoto T, Yoshizawa K, Kubo S, Emoto Y, Hara K, Waters B, et al. Autopsy report for a caffeine intoxication case and review of the current literature. J Toxicol Pathol. 2015;28:33–6.