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Mini-review

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What is more common in fatal caffeine intoxication – suicide or unintentional overdose?

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Caffeine is a natural stimulant of plant origin found in many products such as coffee, tea, chocolate, and energy drinks. It is also often used as an active substance in over-the-counter drugs such as painkillers and preparations for the treatment of colds and allergies. While caffeine is generally considered safe when moderately consumed, excessive intake in a single dose or through repeated small doses over time can lead to caffeine intoxication. Symptoms of caffeine intoxication can vary depending on the amount of caffeine consumed and can include restlessness, rapid heart rate, muscle tremors, nausea, vomiting, and confusion. In severe cases, caffeine intoxication can lead to convulsions, coma, and even death. This mini-review presents an overview of caffeine's characteristics and intoxication including symptoms, causes, diagnosis, and treatment. It addresses risk factors associated with caffeine intoxication and presents current recommendations for safe caffeine consumption. The studies we have reviewed suggest that in cases of fatal caffeine intoxications, intentional intoxication is more common than unintentional.

KEY WORDS: coffee; energy drink; intentional intoxication; unintentional intoxication; over-the-counter drugs

Caffeine is a widely used psychoactive substance found in many drinks and foods such as coffee, tea, chocolate, and energy drinks. It is known for its stimulating effects on the central nervous system (CNS) and is commonly used to improve alertness, cognitive functions, and physical performance. Although drinking coffee is somehow considered a tradition and even has a certain social component, excessive caffeine consumption can lead to caffeine intoxication accompanied by a number of harmful health effects, while in serious cases caffeine intoxication can even be fatal.

Caffeine (1,3,7-trimethylxanthine) is a stimulant found in the seeds, fruits, and leaves of various plants. In addition to coffee and tea, caffeine can be found in cocoa beans, yerba mate leaves, and guarana berries. In plants, caffeine acts as a herbicide and insecticide as well as a pollination attractant. It was first extracted in the 1820s from cocoa beans in its purest form by the German scientist, Friedrich Ferdinand Runge. Caffeine can also be synthesized in the laboratory and synthetic caffeine is used in the food industry and drug production (1–3).

Caffeine belongs to the group of alkaloids, or xanthines, and is a powerful stimulant of the CNS. After ingestion, caffeine is almost completely absorbed within 45 minutes (absorption takes place in the small intestine) and the level of caffeine in the plasma reaches its peak after 15 minutes to 2 hours after ingestion. Caffeine metabolism takes place in the liver by cytochrome P450 oxidase forming three dimethylxanthines: paraxanthine (84 %), theobromine (12 %), and theophylline (4 %). In adults, the half-life of caffeine is 2.5–4.5 h, although the half-life is subject to interindividual variation (1, 3–5).

The U.S. Food and Drug Administration (FDA) classified caffeine as GRAS (Generally Recognized as Safe), in the amount of up to 0.02 % for use in soft drinks. It is important to note that this regulation does not automatically exclude other uses of caffeine from being considered GRAS, but on the other hand, it does not automatically grant GRAS status to other uses and/or higher tolerances (2, 6).

Although caffeine belongs to the GRAS group and long-term use of caffeine in small amounts is safe, some authors have suggested that, despite the certain beneficial effects caffeine has on health, excessive caffeine consumption (1–1.5 g/day) can cause caffeine intoxication (7). Since caffeine is a stimulant with effects on the CNS, the pharmacological effects of caffeine at a plasma concentration of 15 mg/L or more can be manifested in the form of convulsions and cardiac arrhythmias, while concentrations of 80 mg/L or more are considered lethal. Caffeine intoxication is known as "caffeinism", a state of chronic toxicity caused by excessive caffeine consumption. Symptoms of caffeinism include anxiety, agitation, restlessness, insomnia, gastrointestinal disturbances, tremors, psychomotor agitation, and, in some cases, death. Death

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due to caffeine intoxication most often involves taking drugs/dietary supplements containing caffeine, and is a consequence of caffeine's effect on the cardiovascular system (supraventricular and ventricular tachyarrhythmias), and the direct cause of death is often described as ventricular fibrillation (8). However, Lim et al. (9) pointed in their review to the discrepancies in results from clinical studies, elucidating the influence of confounding factors such as gender and smoking status on the outcomes of the reviewed studies, conducted to reveal the actual impact of coffee consumption on cardiovascular disease.

According to the FDA, toxic effects including tachycardia, ventricular arrhythmia, and convulsions have been observed at a dose of approximately 1.2 g, while the life-threatening dose of caffeine is estimated to be 10–14 g, although lower doses may be life-threatening in certain individuals (such as children or other vulnerable populations) (10).

The aim of this article is to present an overview of caffeine intoxication, including symptoms of intoxication, causes, diagnosis, and treatment, and to try to answer the question of whether, in cases resulting with death, unintentional or intentional intoxication is more common.

METHODS AND MATERIALS

By searching the PubMed/MEDLINE database, relevant recent papers published in the period 2013–2024 in English were selected. The key words that were used to search the database included caffeine, caffeine intoxication, lethal effect, death, fatal, caffeine intoxication, intoxication, suicide, acute caffeine intoxication, accidental death, accidental intoxication, and treatment.

Articles that were published in the last 12 years containing key words and available in full text were included. Articles older than 12 years, articles that are not available in full text, articles that are not in English, and articles in which the topic did not correspond to the topic of this review were excluded. According to the same set of key words and inclusive criteria, the MedScape website was also searched, as an aid in the interpretation of the information found in the papers.

DISCUSSION

Persons who intentionally intoxicate themselves most commonly use pharmaceutical or chemical products (11). In addition to food products, caffeine can be found in many over-the-counter (OTC) preparations, such as stimulants, appetite suppressants, decongestants, bronchodilators, pain relievers, nutritional supplements for athletes, and mental stimulants. This increases the risk of toxicity in case of unintentional overuse or severe toxicity in case of intentional overdose (10).

Caffeine acts as an inhibitor of adenosine receptors and phosphodiesterase, which increases the concentration of intracellular calcium, causes the release of noradrenaline and sensitizes dopamine receptors. Studies have shown that it can play a direct or indirect role (in case it is combined with some other substance) in a suicide attempt (12).

According to Murray and Traylor (13), fatal caffeine intoxications in adults are rare and are mostly the result of intentional drug overdoses, while caffeine intoxications in children are mostly the result of unintentional ingestion. Abuse of caffeine (intentional or unintentional) due to the ingestion of products containing it, most often energy drinks or other beverages, is common (14). On the other hand, reports of death resulting from caffeine intoxication are quite rare (15).

Hirose et al. (15) conducted a survey in Japanese suburban adolescents on the frequency of acute intoxication with OTC drugs. The results showed that caffeine (i.e., the drugs containing it) was the cause of intentional fatal intoxication in 54 % of cases (at a dose of 6–21.6 g).

In 2014, Bonsignore et al. (16) reported the case of a 31-year-old man who took a large amount of caffeine tablets (in the form of a dietary supplement) as part of a suicide plan. The case report gives the post mortem biochemical and toxicological analysis, which showed that the caffeine concentration in the femoral blood was 170 mg/L and within the toxic and potentially lethal ranges reported in the literature. Based on the absence of pathological findings at autopsy and high blood caffeine levels, death was attributed to acute caffeine toxicity.

A 2020 US Poison Control Center report listed 2,943 cases of single-dose caffeine intoxication. Of these, 1,912 cases were reported as unintentional intoxication, while 581 cases of intentional intoxication were recorded, of which 15 had a fatal outcome. It should also be noted that 1,791 cases of intoxication in children (0–19 years) were reported, which implies that unintentional intoxications were greater in number (17).

Autopsy findings in caffeine-related deaths are nonspecific and acute toxicity is mostly attributed to adverse cardiovascular events such as ventricular fibrillation and cardiac arrhythmias, whereas caffeine-related deaths are mostly the result of suicide. In a literature review published in 2017, a total of 51 cases of fatal caffeine intoxication were identified, of which 51 % of deaths were the result of suicide (18).

In 2013, Jabbar and Hanly (19) presented the case of a 39-year-old man who committed suicide by ingesting 22 g of pure caffeine, and post mortem blood findings showed a caffeine concentration of 350 mg/L. They also stated in their report that there had been 45 caffeine-related deaths reported in the literature between 1959 and 2010 and 20 of these cases had been reported between 1993 and 2009. Fatalities were reported with doses of 5–50 g of caffeine and death recorded already at blood caffeine concentrations of 80 mg/L.

Yamamoto et al. (20) reported the suicide case of an 18-year-old woman after she ingested 50 g of caffeine. The concentration of caffeine in her blood was 290 mg/L, which was in line with cases described in the literature, although the authors did state that the

autopsy finding was atypical for death caused by caffeine intoxication, as it showed oedematous changes in the brain, which would suggest death due to respiratory arrest caused by functional brain damage caused by caffeine.

Cappelletti et al. (8) reported an increase in deaths related to caffeine intoxication, despite restrictions on the sale of caffeine pills that had been in place in several countries since 2004. In their study, they identified 36 cases of suicide and 27 cases of unintentional intoxication, and the most common route of caffeine administration was oral, while most deaths involved ingestion of large doses of OTC preparations containing caffeine (tablets, powders, liquids).

It is generally accepted that caffeine doses below 400 mg/day are safe and associated with pleasant effects such as alertness, concentration, and relaxation. A sublethal overdose of about 7–10 mg/kg causes anxiety, irritability, nausea, tremors, palpitations, flushing, and headaches. Ingestion of more than 1–2 g of caffeine causes significant toxic effects, while fatal overdoses have been recorded with the ingestion of doses greater than 5 g, i.e., with caffeine blood concentrations greater than 80 mg/L (21). Physical examination findings characteristic of caffeine toxicity include fever, tachycardia or bradycardia, as well as early hypertension followed by hypotension. Pupils may show mydriasis, muscles may be rigid, and deep tendon reflexes may be accentuated (hyperreflexia). Neurologic examinations may show altered mental status, agitation, delusions, hallucinations, convulsions, or even focal neurologic findings thought to be due to ischemia following vasoconstriction. The patients usually feel nauseous and often vomit (13).

Treatment of caffeine intoxication depends on the clinical picture. The first step is the assessment of vital parameters, intravenous replacement of fluids and electrolytes, and symptomatic therapy according to the presented symptoms. Oral administration of activated charcoal can also contribute to lowering blood caffeine levels via enterohepatic circulation, as can intravenous administration of lipid emulsions. In cases of severe intoxication, haemodialysis is the method of choice for removing caffeine from the body, along with other intensive treatment procedures and monitoring in the intensive care unit (13, 21, 22). Sometimes, even the regulatory approach to involuntary caffeine intoxication has to be taken into account, given that the term "involuntary intoxication" is defined variably. An appropriate description was given in Hearn et al. (23), who presented a case in which a defendant ingested large quantities of caffeine, which resulted in transient psychosis and a successful affirmative defence of involuntary intoxication.

In 2015, the EFSA published guidelines on the recommended doses of caffeine, based on a risk assessment analysis. They stated that single doses of 200 mg (about 3 mg/kg) do not pose a risk to a healthy adult. Single doses of 100 mg (about 1.4 mg/kg) of caffeine may affect the duration and patterns of sleep in some adults, particularly if consumed shortly before bedtime. Intakes of up to 400 mg per day (about 5.7 mg/kg per day) do not pose a risk to healthy adults, except for pregnant women (a daily dose of up to 200 mg is considered safe). An amount of 3 mg/kg of body weight per day is considered safe for children and adolescents (24).

CONCLUSION

Caffeine is a psychoactive substance of plant origin, the consumption of which is generally culturally and socially accepted. In addition to food products, caffeine is found as an active substance in drugs, nutritional supplements for athletes, various beverages, and cosmetics. Although serious and fatal caffeine intoxications are rare, the abuse of caffeine is on the rise, and it is primarily associated with the greater availability of different formulations (often of questionable composition and origin) and with the lack of education of the wider population about the potential harmful effects of excessive caffeine consumption, as well as with the lack of information about the caffeine content in certain products.

By reviewing the literature that was used to create this paper, we can conclude that, although rare, fatal caffeine intoxications are mostly the result of intentional intoxication, most often in a suicide attempt. Older people and young children, as well as athletes and people suffering from mental illnesses, are at greater risk of caffeine intoxication.

The problem in the increasing abuse of caffeine, which results in an increase in reported cases of intoxication, probably lies in (1) the availability of various caffeine preparations given over the counter, (2) the large amount of information about the toxicity of caffeine that is available to people with suicidal intentions, and (3) the unregulated market of dietary supplements and lack of stricter controls. Also, the problem with dietary supplements based on caffeine or pure caffeine lies in the fact that they are generally available in large quantities and the consumer is required to assess the exact dose to be used, which can often result in unintentional caffeine intoxication, while on the other hand it makes it easier for people to access a potentially lethal substance with suicidal intent. Caffeine intoxication, and even deaths caused by it, could be reduced by stricter controls regarding food supplements and pure caffeine preparations, by limiting the amount of food supplements that can be bought simultaneously, by campaigns aimed at educating the population about the effects of caffeine on the body, as well as by limiting the marketing of products with high caffeine content. Also, although such products usually have warnings about caffeine content, they are available over the counter and there is no age limit for purchasing such products, therefore setting an age limit could also contribute to reducing the incidence of caffeine intoxication. Reducing the risk of caffeine intoxication can be achieved by limiting caffeine intake and carefully choosing the foods that are consumed. One must be aware of the caffeine content in certain food products and medicines and nutritional supplements. As far as fatal caffeine intoxication is concerned, intentional intoxication is more common.

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Conflicts of interest

The authors declare no conflict of interest.

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Otrovanje kofeinom sa smrtnim ishodom – je li češće samoubojstvo ili slučajno predoziranje?

Kofein je prirodni stimulans biljnog podrijetla koji se nalazi u mnogim prehrambenim proizvodima poput kave, čaja, čokolade i energetskih napitaka. Također, često se koristi kao jedna od aktivnih tvari u bezreceptnim lijekovima poput lijekova protiv bolova i pripravaka za liječenje prehlade i alergija. Dok se kofein općenito smatra sigurnim ako se umjereno konzumira, pretjerani unos u jednoj dozi ili ponavljanim malim dozama tijekom vremena može dovesti do otrovanja kofeinom. Simptomi otrovanja kofeinom ovise o količini konzumiranog kofeina i mogu uključivati nemir, ubrzan rad srca, drhtanje, mučninu, povraćanje i zbunjenost. Teški slučajevi otrovanja kofeinom moge dovesti do konvulzija, kome, pa čak i smrti. U ovom su preglednom radu prikazane karakteristike otrovanja kofeinom uključujući uzroke, simptome, dijagnozu i liječenje. Opisani su čimbenici rizika povezani s otrovanjem kofeinom te navedene trenutne preporuke za sigurnu konzumaciju kofeina. Iz rezultata objavljenih istraživanja prikazanih u ovome preglednom radu može se zaključiti da je u slučajevima smrtonosnih otrovanja kofeinom, namjerno otrovanje češće nego slučajno.

KLJUČNE RIJEČI: bezreceptni lijek; energetski napitak; kava; namjerno otrovanje; slučajno otrovanje