Forensic Sci Med Pathol
DOI 10.1007/s12024-016-9786-9

REVIEW

Caffeine toxicity in forensic practice: possible effects and under-appreciated sources

Ian F. Musgrave[1,2] · Rachael L. Farrington[1] · Claire Hoban[1] · Roger W. Byard[2]

Accepted: 8 June 2016

Abstract Caffeine is considered a very safe stimulant and is widely consumed in a variety of forms, from pure caffeine to beverages and foods. Typically, death is only seen when gram quantities of caffeine are consumed, usually in suicide attempts. Even in this scenario, death is rare. However, there are special populations that need to be considered in forensic presentations, who may be at greater risk. These include poor metabolizers, people with liver disease, and people with cardiac conditions, who can die as a result of caffeine intake at levels well below what is ordinarily considered toxic. Also, caffeine intake may be hidden. For example, herbal medicines with substantial caffeine content may not disclose these concentrations on their product label. The role of caffeine in medicolegal deaths is yet to be defined, however, herbal medicines and herbal weight loss supplements may represent an under-appreciated source of caffeine in this context.

Keywords Caffeine · Toxicity · Forensic · Death · Caffeine-intoxication · Herbal medicine · Pharmacokinetics · Undeclared sources · Review

✉ Ian F. Musgrave
ian.musgrave@adelaide.edu.au

[1] Discipline of Pharmacology, The University of Adelaide, Frome Road, Level 5 Medical School North Building, Adelaide, SA 5005, Australia

[2] Discipline of Anatomy and Pathology, School of Medicine, The University of Adelaide, Frome Road, Level 3 Medical School North Building, Adelaide, SA 5005, Australia

Introduction

Caffeine is a naturally occurring alkaloid (1,3,7-trimethylxanthine) that is found in a wide variety of plants. It is one of the most widely consumed stimulants and decoctions of caffeine containing plants are used as beverages or incorporated into foods world-wide. Caffeine acts as a stimulant on the central nervous and cardiovascular systems, primarily through blockade of inhibitory adenosine receptors at lower doses, and inhibition of phosphodiesterases at higher doses [1, 2].

While modest caffeine intake is generally recognized as safe, and may have health benefits [3, 4], higher intakes are associated with adverse effects such as tachycardia, nausea, and vomiting [2, 5]. Death has also been associated with excessive consumption. The contribution of caffeine to mortality in a forensic context has not, however, been extensively investigated and its role as a risk modifier in individuals with underlying central nervous system or cardiovascular disorders is unclear. Interactions between caffeine and other components of caffeine-containing products can also increase the risk of adverse effects. Finally, the amounts of caffeine in a product can be difficult to determine for consumers, particularly when it is undeclared in products such as weight loss supplements and herbal medicines, or in the form of caffeine containing plant additives such as guarana [6], yerba matte, and green tea.

Caffeine intake

Caffeine can be consumed in a variety of forms. It is present in beverages (teas, coffee, colas, cocoa, energy drinks), foods (chocolate, ice-creams, various deserts,

Published online: 25 June 2016

Table 1 Typical caffeine contents of a variety of caffeine-containing products

Caffeine sources	Typical caffeine content
Caffeine tablets	100–200 mg caffeine per tablet
Caffeine strips	40 mg caffeine per strip
Caffeine containing analgesics	32–65 mg caffeine per dose
Weight loss products	6–200 mg caffeine per dose
Herbals other than weight loss products	5–100 mg caffeine per dose
Body building products	100–300 mg caffeine per dose
Energy drinks	80–160 mg caffeine per serve
Chocolate	70–198 mg per 100 g
Average espresso	75–85 mg caffeine
Instant coffee	~65 mg caffeine
Tea	50–80 mg caffeine
375 ml iced coffee	68 mg caffeine
Colas	30–70 mg caffeine

These values were obtained from a variety of sources, including manufactures sites and packaging. The caffeine content of teas and coffee can vary substantially depending on how it is brewed and the type of leaf or bean used

mints, and caffeine containing strips), weight loss supplements, herbal medicines, in some analgesic preparations, and some body building supplements. It may also be mixed with illicit drugs or taken on its own in pill or capsule form.

Examples of the caffeine content of certain drinks/products are shown in Table 1.

Caffeine toxicity

For a healthy individual with no heart disease or altered pharmacokinetics, consumption of 200 mg or less of caffeine is not usually associated with toxic effects [1]. Intakes of between 100 and 200 mg caffeine in one dose are commonly used by athletes as performance enhancers [7]. While there is no generally recognized safe level of caffeine intake, the European Food Safety Authority has recommended 400 mg/day as the maximum safe level for healthy non-pregnant adults, 200 mg/day for healthy pregnant women, and 3 mg/kg body weight per day as a provisional intake for children [1].

Taking more than 300 mg of caffeine at once can result in caffeine intoxication (DSM-IV 305.90). The symptoms largely reflect its stimulant action and may include restlessness, nervousness, excitement, insomnia, flushing of the face, increased urination, gastrointestinal disturbance, muscle twitching, a rambling flow of thought and speech, irritability, arrhythmia, tachycardia, and psychomotor agitation [2, 5]. Tachycardia, nausea, vomiting, and cerebral edema have also been reported [8] as have seizures [9].

The severity of the adverse effects of caffeine ingestion is dose dependent. In a study of people who were admitted to emergency wards in New South Wales, Australia, after drinking energy drinks, the commonest symptoms involved palpitations/tachycardia, tremor/shaking, agitation/restlessness, and gastrointestinal upset. The median caffeine consumption was 400 mg [8]. With ingestion of 1–2 g of caffeine, the most common problems involve seizures or arrhythmias [2, 5, 10]. Finally, death has been reported with ingestion of 5–10 g of caffeine [2, 11–15]. However, these broad dose ranges for intoxication can be significantly influenced by variations in caffeine metabolism, disease states, and caffeine-drug interactions.

Caffeine metabolism

Caffeine is primarily (90 %) cleared by the liver via the cytochrome P4501A2 system [16]. There is, however, great variability in the clearance of caffeine between individuals (up to 40-fold [17]), largely due to polymorphisms in the CYP1A2 enzyme [17, 18]. These polymorphisms not only affect plasma clearance of caffeine, but may also affect other pharmacokinetic aspects such as the response to enzyme inducers. This means that poor metabolizers of caffeine may be exposed to higher plasma concentrations from equivalent intakes. Around 40 % of Caucasians have a version of the CYP1A2 enzyme that breaks down caffeine slowly. In these people, caffeine consumption is correlated with higher incidences of ischemic heart disease [19] and hypertension [20], both of which are disorders associated with sudden and unexpected death, and therefore frequently encountered in medicolegal cases. The role of CYP1A2 polymorphisms in adverse reactions to caffeine has been minimally explored. However, a recent Australian survey showed that people were calling a poisons information center after ingesting as little as 150 mg of caffeine in energy drinks [8]. Furthermore, in presentations to an Australian emergency department, palpitations were associated with an average daily consumption of 1.7 energy drinks per day [21]. This suggests that pharmacokinetic variation may be important in responses to caffeine ingestion.

Caffeine metabolism in disease

Hepatic disease can slow caffeine metabolism. For example, both cirrhosis and hepatitis reduce CYP1A2 levels, with a resultant reduction in the clearance of caffeine [22]. Another example of the impact of hepatic disease on acute caffeine toxicity was a death resulting from the ingestion of caffeine containing mints. Although the number of mints ingested should not have been lethal, the decedent had

cirrhosis, which resulted in high plasma caffeine concentrations [23].

Caffeine metabolism–drug interactions

Numerous drugs can interfere with caffeine metabolism. Of particular concern are cardiovascular drugs such as propafenone, mexiletine, and verapamil [24] which inhibit caffeine metabolism. Caffeine clearance is also decreased by 36 % with chronic alcohol consumption [25]. As noted above increased amounts of caffeine in people with cardiac risk factors are of concern.

Caffeine toxicity: case studies

Death from acute caffeine toxicity is rare and usually involves either deliberate or accidental overdose, with the ingestion of substantial amounts (grams) [13–15, 26]. Despite the deliberate ingestion of large quantities of caffeine a recent review found that only 7 of 15 such suicide attempts were successful [14]. The mechanism of death in fatalities from caffeine overdose often involves concomitant disease (typically cardiovascular, but cirrhosis and hepatitis are also reported), combinations with other drugs, or both of these factors [10, 11, 27].

However, examples of fatalities due to caffeine ingestion exist where the amounts of ingestion were relatively low. In one case a 25 year old woman with mitral valve prolapse died of ventricular arrhythmia after consuming no more than 550 mg of caffeine from an energy drink [10], well below the amounts normally seen in fatal overdoses.

In contrast a 28 year old man suffered cardiac arrest after consuming up to 640 mg of caffeine from energy drinks while performing strenuous exercise [28]. The person had been healthy with no sign of previously unrecognized heart disease.

In some cases lower amounts of caffeine may contribute to the toxicity of other drugs. For example, a case of severe rhabdomyolysis in a marathon runner was attributed to the interaction between ephedrine (60 mg), caffeine (240 mg) and aspirin (60 mg) [29].

Significant toxicity without death has been reported in a number of studies and case reports [5, 8–10, 30–33]. Typically cardiovascular, central nervous system and liver toxicity are reported. In rare cases rhabdomyolysis has been reported attributable to caffeine alone [34, 35]. Energy drinks in particular have come under scrutiny because of their perceived potential for abuse, but other sources include caffeine in illicit drugs, as yet legally available "highs", weight loss supplements, and herbal medicines [8–10, 26, 30, 31, 33, 36–39].

Forensic detection of caffeine

There are multiple methods of detecting caffeine in bodily fluids. Typically high performance liquid chromatography with ultraviolet detection [11, 12] or gas chromatography with mass spectrometry is used [11–13, 15]. Routine screening for caffeine is typically not performed in most jurisdictions although there are exceptions (for example see [40]). Given the increasing exposure to caffeine from energy drinks, and other sources, Jabbar and Hanley [13] have called for routine caffeine screening. Blood concentrations associated with death have been reported in the ranges of 33–1560 mg/L [11–13, 15, 27]. While blood concentrations of > 80 mg caffeine/L are considered lethal [11, 12, 15], lower concentrations can be associated with lethality if the decedent has underlying pathology (e.g. dilated cardiomyopathy 49 mg/L [11]). Postmortem caffeine concentrations are typically similar in right heart blood compared to peripheral blood and urine [11, 41, 42], and lower in the CSF [41, 43]. Tissue concentrations are less well studied, but caffeine levels in the brain, heart, and muscle have been reported to be similar to those in right heart blood, while levels in the lung are higher [15, 41]. However, in one case, the caffeine levels in the brain and lung were substantially higher than blood levels [11].

Undeclared caffeine

Herbal medicines are of particular concern because of their perceived safety and their use in a medical, rather than a recreational context [33, 44]. While in many jurisdictions, the contents of herbal medicines and weight loss supplements are required to be shown on labels, this may not reflect the actual content. For example, the supplement or medicine may correctly list ingredients such as *Camellia sinensis*, *Coffea canephora* or *Paullinia cupana* but not the actual caffeine content. As well, the Latin botanical names for green tea, coffee beans and guarana may be misleading to consumers who may not associate them with the common names of these caffeine containing beverages.

In other cases caffeine may be added surreptitiously. In one survey of herbal medicines for weight loss, six of nine products had been adulterated with undeclared caffeine [45], and in another series four of eight weight loss herbal medicines contained undeclared caffeine [46].

The amount of undeclared caffeine was not reported in the two studies above, which focused on other adulterants. Concentrations of declared caffeine in herbal medicines range from 5 to 100 mg per capsule, so it is possible that someone taking supplements with undeclared caffeine could ingest up to 180 mg of caffeine a day depending on the dosing regime. With concomitant consumption of three

espresso coffees and other dietary sources of caffeine, the recommended limit of 400 mg caffeine per day would be easily reached. People who binge on weight loss preparations to control weight would be at even higher risk [30]. For people who have cardiovascular disease (especially those taking drugs which inhibit caffeine metabolism), liver disease, CYP1A2 polymorphisms, or susceptibility to seizures, an inadvertent intake of caffeine of 400 mg per day could have serious consequences [9, 10].

Hidden in plain sight

Although products may declare caffeine content on their labels and even have consumption warnings on them, these warnings may be unseen or ignored. In the case the of death resulting from the ingestion of caffeine containing mints [23], the container not only had the caffeine content displayed on the back, but also advice not to consume more than 5 mints in 24 h [23]. Yet the decedent consumed significantly more than the recommended level.

Depending on the jurisdiction, most typical energy drinks will have on the containers a recommended daily maximum energy drink intake of 2 × 250 or 1 × 500 mL. However, consumption levels can far exceed this; for example, callers to the NSW Poisons Information Centre had a median intake of 5 energy drinks, with the highest consumption being 80 energy drinks [8].

Consumers of weight loss products [30] and body building products may also consume more than the recommended dosing levels and expose themselves to the risk of caffeine toxicity.

Conclusions

Caffeine is generally recognized as a very safe stimulant, with death or serious toxic reactions only occurring with very high doses, usually taken deliberately. However, for people who have impaired caffeine metabolism or who suffer from medical conditions that may be exacerbated by lower amounts of caffeine, adverse events may occur with apparently standard intakes. Inadvertent consumption of caffeine may be a significant concern in these populations. While there has been a focus on energy drinks, especially when consumed under conditions where their intake may not be well controlled, herbal medicines and herbal weight loss supplements could represent another underappreciated source of caffeine. This is particularly so with preparations that contain undeclared amounts of caffeine. The role of caffeine in medicolegal deaths is yet to be defined.

Key points

1. Caffeine is generally recognized as a safe stimulant.
2. Individuals who have cardiovascular disease, or who have poor methylxanthine metabolism, are at higher risk of caffeine toxicity.
3. Products with undeclared caffeine, such as some herbal medicines, can be an unrecognized source of caffeine intoxication.
4. The role of caffeine in medicolegal deaths is yet to be defined.

References

1. Panel EN. Scientific opinion on the safety of caffeine. EFSA J. 2015;13:120.
2. Dalvi RR. Acute and chronic toxicity of caffeine: a review. Vet Hum Toxicol. 1986;28:144–50.
3. Crippa A, Discacciati A, Larsson SC, Wolk A, Orsini N. Coffee consumption and mortality from all causes, cardiovascular disease, and cancer: a dose-response meta-analysis. Am J Epidemiol. 2014;180:763–75.
4. Loftfield E, Freedman ND, Graubard BI, Guertin KA, Black A, Huang WY, et al. Association of Coffee consumption with overall and cause-specific mortality in a large US prospective cohort study. Am J Epidemiol. 2015;182:1010–22.
5. Boison D. Methylxanthines, seizures, and excitotoxicity. Handb Exp Pharmacol. 2011;200:251–66.
6. Schimpl FC, da Silva JF, Goncalves JF, Mazzafera P. Guarana: revisiting a highly caffeinated plant from the Amazon. J Ethnopharmacol. 2013;150:14–31.
7. Tunnicliffe JM, Erdman KA, Reimer RA, Lun V, Shearer J. Consumption of dietary caffeine and coffee in physically active populations: physiological interactions. Appl Physiol Nutr Metab. 2008;33:1301–10.
8. Gunja N, Brown JA. Energy drinks: health risks and toxicity. Med J Aust. 2012;196:46–9.
9. Pendleton M, Brown S, Thomas CM, Odle B. Potential toxicity of caffeine when used as a dietary supplement for weight loss. J Diet Suppl. 2013;10:1–5.
10. Cannon ME, Cooke CT, McCarthy JS. Caffeine-induced cardiac arrhythmia: an unrecognised danger of healthfood products. Med J Aust. 2001;174:520–1.
11. 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.
12. Bonsignore A, Sblano S, Pozzi F, Ventura F, Dell'Erba A, Palmiere C. A case of suicide by ingestion of caffeine. Forensic Sci Med Pathol. 2014;10:448–51.
13. Jabbar SB, Hanly MG. Fatal caffeine overdose: a case report and review of literature. Am J Forensic Med Pathol. 2013;34:321–4.
14. Silva AC, de Oliveira Ribeiro NP, de Mello Schier AR, Pereira VM, Vilarim MM, Pessoa TM, et al. Caffeine and suicide: a systematic review. CNS Neurol Disord: Drug Targets. 2014;13:937–44.
15. 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.

16. Dorne JL, Walton K, Renwick AG. Uncertainty factors for chemical risk assessment: human variability in the pharmacokinetics of CYP1A2 probe substrates. Food Chem Toxicol. 2001;39:681–96.
17. Kashuba AD, Bertino JS Jr, Kearns GL, Leeder JS, James AW, Gotschall R, et al. Quantitation of three-month intraindividual variability and influence of sex and menstrual cycle phase on CYP1A2, N-acetyltransferase-2, and xanthine oxidase activity determined with caffeine phenotyping. Clin Pharmacol Ther. 1998;63:540–51.
18. Wang L, Hu Z, Deng X, Wang Y, Zhang Z, Cheng ZN. Association between common CYP1A2 polymorphisms and theophylline metabolism in non-smoking healthy volunteers. Basic Clin Pharmacol Toxicol. 2013;112:257–63.
19. Cornelis MC, El-Sohemy A, Kabagambe EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. JAMA. 2006;295:1135–41.
20. Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine. Psychopharmacology. 2010;211:245–57.
21. Busuttil M, Willoughby S. A survey of energy drink consumption among young patients presenting to the emergency department with the symptom of palpitations. Int J Cardiol. 2016;204:55–6.
22. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol. 2008;64:1147–61.
23. Cheston P, Smith L. Man died after overdosing on caffeine mints. Independent. 2013.
24. Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. Clin Pharmacokinet. 2000;39:127–53.
25. George J, Murphy T, Roberts R, Cooksley WG, Halliday JW, Powell LW. Influence of alcohol and caffeine consumption on caffeine elimination. Clin Exp Pharmacol Physiol. 1986;13:731–6.
26. Ciszowski K, Biedron W, Gomolka E. Acute caffeine poisoning resulting in atrial fibrillation after guarana extract overdose. Przegl Lek. 2014;71:495–8.
27. Bryczkowski C, Geib AJ. Combined butalbital/acetaminophen/caffeine overdose: case files of the Robert Wood Johnson Medical School Toxicology Service. J Med Toxicol. 2012;8:424–31.
28. Berger AJ, Alford K. Cardiac arrest in a young man following excess consumption of caffeinated "energy drinks". Med J Aust. 2009;190:41–3.
29. Rhidian R. Running a risk? Sport supplement toxicity with ephedrine in an amateur marathon runner, with subsequent rhabdomyolysis. BMJ Case Rep. 2011. doi:10.1136/bcr.11.2011.5093.
30. Berger RE, Ganetsky M. An over-the-counter weight-loss supplement with a toxicity that may be unexpectedly difficult to treat. Intern Emerg Med. 2012;7(Suppl 2):S91–2.
31. Seifert SM, Seifert SA, Schaechter JL, Bronstein AC, Benson BE, Hershorin ER, et al. An analysis of energy-drink toxicity in the National Poison Data System. Clin Toxicol (Phila). 2013;51:566–74.
32. Wolk BJ, Ganetsky M, Babu KM. Toxicity of energy drinks. Curr Opin Pediatr. 2012;24:243–51.
33. Yen M, Ewald MB. Toxicity of weight loss agents. J Med Toxicol. 2012;8:145–52.
34. Campana C, Griffin PL, Simon EL. Caffeine overdose resulting in severe rhabdomyolysis and acute renal failure. Am J Emerg Med. 2014;32:111.e3–.e4.
35. Chiang WF, Liao MT, Cheng CJ, Lin SH. Rhabdomyolysis induced by excessive coffee drinking. Hum Exp Toxicol. 2014;33:878–81.
36. Cole C, Jones L, McVeigh J, Kicman A, Syed Q, Bellis M. Adulterants in illicit drugs: a review of empirical evidence. Drug Test Anal. 2011;3:89–96.
37. Davies S, Lee T, Ramsey J, Dargan PI, Wood DM. Risk of caffeine toxicity associated with the use of 'legal highs' (novel psychoactive substances). Eur J Clin Pharmacol. 2012;68:435–9.
38. Hoyte C. The toxicity of energy drinks: myth or reality? Clin Toxicol (Phila). 2013;51:729–30.
39. O'Malley PA. Caffeinated energy drinks: risks assumed with consumption when competing, working, and drinking. Clin Nurse Spec. 2012;26:250–3.
40. Suzuki H, Tanifuji T, Abe N, Maeda M, Kato Y, Shibata M, Fukunaga T. Characteristics of caffeine intoxication-related death in Tokyo, Japan, between 2008 and 2013. Nihon Arukoru Yakubutsu Igakkai Zasshi. 2014;49:270–7.
41. Ishikawa T, Yuasa I, Endoh M. Non specific drug distribution in an autopsy case report of fatal caffeine intoxication. Leg Med (Tokyo). 2015;17:535–8.
42. Tominaga M, Michiue T, Oritani S, Ishikawa T, Maeda H. Evaluation of postmortem drug concentrations in bile compared with blood and urine in forensic autopsy cases. J Anal Toxicol. 2016;40:367–73.
43. Tominaga M, Michiue T, Ishikawa T, Inamori-Kawamoto O, Oritani S, Maeda H. Evaluation of postmortem drug concentrations in cerebrospinal fluid compared with blood and pericardial fluid. Forensic Sci Int. 2015;254:118–25.
44. Byard RW. The potential forensic significance of traditional herbal medicines. J Forensic Sci. 2010;55:89–92.
45. Ozdemir B, Sahin I, Kapucu H, Celbis O, Karakoc Y, Erdogan S, et al. How safe is the use of herbal weight-loss products sold over the internet? Hum Exp Toxicol. 2013;32:101–6.
46. Khazan M, Hedayati M, Kobarfard F, Askari S, Azizi F. Identification and determination of synthetic pharmaceuticals as adulterants in eight common herbal weight loss supplements. Iran Red Crescent Med J. 2014;16:e15344.