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Review

Review

Review of Caffeine-Related Fatalities along with Postmortem Blood Concentrations in 51 Poisoning Deaths

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Abstract

Publications reporting concentrations of caffeine in postmortem blood were reviewed if the cause of death was attributed to overdosing (poisoning) with drugs. Age and gender of the deceased, the manner of death (accident, suicide or undetermined) and types of co-ingested drugs were evaluated in relation to the concentrations of caffeine in blood ($N = 51$). The mean age (±SD) of the victims was 39 ± 17.8 years (range 18–84 years) and most were female ($N = 31$ or 61%). The difference in mean age of males (42 ± 17.2 years) and females (37 ± 18.3 years) was not statistically significant ($t = 0.811$, $P = 0.421$). The mean (±SD), median and range of caffeine concentrations in postmortem blood were 187 ± 96 mg/L (180 mg/L) and 33–567 mg/L, respectively. The median concentration of caffeine in males (161 mg/L) was not significantly different from that of females (182 mg/L), $z = 1.18$, $P = 0.235$. There was no correlation between the age of the deceased and the concentration of caffeine in postmortem blood ($R^2 = 0.026$, $P > 0.05$). Manner of death was classified as suicide in 51% of cases (median blood–caffeine 185 mg/L), accidental in 16% (median 183 mg/L) or undetermined in 33% (median 113 mg/L). The median concentration of caffeine in blood was lower when manner of death was undetermined compared with suicide or accidental ($P = 0.023$). Although other drugs, including ethanol, antidepressants, antipsychotics, benzodiazepines and/or ephedrine, were often identified in postmortem blood, the predominant psychoactive substance was caffeine. The deceased had ingested caffeine in tablet or powder form and it does not seem likely that toxic concentrations of caffeine can be achieved from over-consumption of caffeinated beverages alone.

Introduction

Caffeine is a relatively innocuous drug, but to paraphrase a statement made by Paracelsus (1492–1541) ~500 years ago, "Solely the dose determines that a thing is not a poison" (1). This implies that overdosing with caffeine, like anything else, can lead to toxicity and death. After drinking a caffeinated beverage, the pharmacologically active drug is rapidly absorbed into the blood and easily passes the blood–brain barrier to function as a mild stimulant of the central nervous system (2, 3).

The amounts of caffeine contained in coffee, tea, soft-drinks and energy-drinks vary depending on the source and method of preparation as well as the volume of a typical serving. Most caffeinated beverages contain between 50 and 100 mg caffeine, which seems to be an average amount per drink (4). Caffeine is also available in powder or tablet form without a doctor's prescription and people use the drug as an appetite suppressant, to help stay awake longer (counteract fatigue), to boost energy and increase alertness by functioning as a general pick-me-up (5). Caffeine is sold over-the- counter in combination with other substances, such as ephedrine, theophylline or aspirin, and these preparations might contain between 100 and 200 mg of caffeine per tablet.

Millions of people drink several cups of coffee or tea daily without any ill effects, although after chronic consumption some susceptible individuals run the risk of habituation and concomitant dependence on caffeine (6, 7). The popularity of mixing caffeine-rich energy-drinks with alcohol has raised some concern, owing to a perceived enhanced

toxicity (8, 9). However, expert opinions and publications about the health hazards of drinking energy-drinks alone or together with alcohol are divided (10, 11).

Because of the popularity of caffeinated drinks in society one can expect to find measurable concentrations of caffeine in blood from a randomly selected person (12). To avoid reporting insignificant (therapeutic) concentrations of caffeine in routine casework, most forensic toxicology laboratories use a relatively high analytical cut-off concentration, such as 5–10 mg/L to report positive results.

This article reports caffeine concentrations in postmortem blood from 51 caffeine-related poisoning deaths when the analytical method used was gas chromatography (GC). The results are discussed in relation to age and gender of the deceased, the role of co-ingested drugs and the manner of death according to the medical examiner reports.

Methods

Original publications and case reports of caffeine-related deaths were identified from searching PUBMED and also by scanning individual journals specializing in analytical toxicology, forensic science, legal medicine and clinical toxicology. This search strategy located 51 well-documented intoxication deaths where caffeine was the main psychoactive substance in postmortem blood. The concentrations of caffeine and other drugs in blood, the age and gender of the deceased and the manner of death (accident, suicide or undetermined) were available for scrutiny.

Femoral blood was used for toxicological analysis in 25 caffeine-related deaths and in 19 cases cardiac blood was taken for analysis. In the remaining seven cases the source of blood was not mentioned in the published article. In four caffeine-related deaths both central and peripheral blood samples were available for forensic analysis (13).

Also reviewed were papers reporting the caffeine content of various caffeinated drinks, including coffees, teas, soft-drinks and energy-drinks (14–17). This was considered relevant to help interpret concentrations of caffeine in blood in the poisoning deaths. Likewise, studies of the pharmacokinetics of caffeine were reviewed to document relevant kinetic parameters, such as plasma elimination half-life and volume of distribution.

Some of the articles contained information from a single caffeine-related poisoning death whereas others included 2–4 victims (18–23). By far the largest case series, which comprised 20 caffeine intoxication deaths, came from Sweden (24). Fatalities were also reported from other countries, such as Japan (25), USA (13, 26), Germany (27) and Italy (28).

Results

Caffeine content in drinks

Caffeinated beverages are ubiquitous in society and millions of people drink coffee, tea, soft-drinks and energy-drinks daily (29). The caffeine contained in a large selection of such drinks was determined after liquid–liquid extraction and use of capillary GC with a nitrogen–phosphorous (N–P) detector (14–17). These concentrations of caffeine are summarized in Table I. The GC method with N–P detector is well-established in analytical toxicology and with slight modifications was also used to determine caffeine in forensic blood samples (30).

The caffeine content of energy-drinks ranged from 0 to 77 mg/240 mL per serving, whereas 360 mL of carbonated sodas contained 0–48 mg of caffeine (17). Other beverages, such as ice-tea and various commercially available brewed coffees contained 3–106 mg caffeine per 210 mL or 480 mL servings (16). Another study reported that 10 types of energy drink (240 mL volumes) contained between 65 and 126 mg caffeine (30). Coffee advertised and sold as decaffeinated did contain small amounts of caffeine, such as 18 mg/serving (15). This compares with 58–258 mg/serving in caffeinated coffees from different manufacturers and commercial outlets (16). Depending on the method of preparation, a regular size serving of coffee might contain ~100 mg caffeine on the average.

Table I. Caffeine content of various commercially available caffeinated beverages determined after solvent extraction and GC analysis with N–P detector (14–17)

Caffeinated beverage	Caffeine content in volume of typical servings[a]
Various energy-drinks	0–141 mg
Carbonated sodas	0–48 mg
Other soft-drinks	3–106 mg
Coca Cola[b]	41–48 mg
Specialty coffees	58–259 mg
Decaffeinated coffee	0–14 mg
Teas (white, green or black)	14–61 mg

[a]Typical servings are 480 mL for coffees, 240 mL for teas and 240–360 mL for energy-drinks and sodas.

[b]Based on 480 mL servings purchased from 9 different outlets.

Pharmacokinetics of caffeine

After drinking a caffeinated beverage, the caffeine they contain is rapidly absorbed from the stomach and intestines and the peak concentrations in blood or plasma are reached 30–90 min post-dosing (2). The clinical pharmacokinetics of caffeine (1,3,7-trimethylxanthine) in adults was dose-dependent and after large doses zero-order kinetics occur, because the metabolizing enzymes are saturated with substrate (31). In several human dosing studies, the systemic bioavailability of caffeine was close to 100% indicating that first-pass metabolism is negligible (31–33). Caffeine is extensively metabolized and only ~3% of the dose is excreted unchanged in the urine (34).

After absorption into the blood, caffeine distributes into the total body water compartment and the volume of distribution is within the range 0.6–0.7 L/kg. The plasma elimination half-life of caffeine in adults ranges from 3 to 7 h, although clearance rates are slower in neonates, owing to late development of certain hepatic enzymes. Caffeine undergoes N-demethylation by the action of hepatic cytochrome P4501A2 (CYP1A2) to give three primary metabolites, paraxanthine, theobromine and theophylline. The CYP1A2 enzyme exhibits polymorphism, which makes it likely that genetic factors might account for some of the observed inter-individual variations in plasma pharmacokinetic profiles and elimination half-life of caffeine (35, 36). Furthermore, clearance of caffeine might be slower in people with hepatic dysfunction.

Caffeine easily crosses the blood–brain barrier and acts as antagonist at receptor sites for the neurotransmitter adenosine (37). Overdosing with caffeine causes excitement, agitation and people experience tachycardia, heart palpitations and often require emergency hospital treatment (38, 39).

Caffeine-related deaths

The autopsy findings in caffeine-related deaths are non-specific and acute toxicity is mostly ascribed to adverse cardiovascular events,

including cardiac arrhythmias and development of ventricular fibrillations (24, 40). Elderly and frail people might be more susceptible to the toxic effects of overdosing with caffeine than younger more healthy individuals. High doses of caffeine are likely to cause seizures and may need emergency medical treatment (39).

The available clinical and forensic toxicology literature contain well-documented reports of caffeine-related poisoning deaths, mostly in suicide attempts (41). Caffeine tablets are available in most nations as an over-the-counter mild stimulant or pick-me-up. After four deaths were reported in Sweden, the regulatory authorities issued warnings and the number of tablets that could be purchased at one time was restricted, although a follow-up study showed that overdosing with caffeine still continued (42). A detailed clinical course and the life-saving treatment was presented for a 21-year-old female who attempted suicide by swallowing 100 caffeine tablets, but she had second thoughts and called emergency medical services (24).

All the articles reviewed used GC methods of analysis and information was available about the victims age and gender, the manner of death according to medical examiner report and the concentration of caffeine in postmortem blood (13, 19, 20, 26, 28). When the victims were admitted to hospital for treatment, the typical signs and symptoms reported were agitation, excitement, rapid and erratic heat rhythm, respiratory distress, convulsions and entering a comatose state before cessation of breathing (39).

Demographics of victims

Table II presents age and gender of the deceased in relation to the concentrations of caffeine in postmortem blood. Most victims were female (61%), although there was no significant difference in mean age in relation to gender ($t = 0.811$, $P = 0.421$). Neither did the mean (median) concentration of caffeine in blood depend on gender ♂ = 183 ± 118 mg/L (162 mg/L) and ♀ = 190 ± 82 mg/L (182 mg/L). The median values were not significantly different according to non-parametric Mann–Whitney U-test ($z = 1.187$, $P = 0.235$).

Figure 1 shows a lack of correlation (R^2 coefficient of determination = 0.026) between victims age and the concentration of caffeine in postmortem blood. In this case series of 51 deaths the age of the victims ranged from 18 to 84 years and 6 (12%) were above the age of 60 years. Whether some natural disease, such as compromised cardiovascular and/or respiratory function, might have been a contributing factor in their deaths is not known. However, the mean blood–caffeine concentration in people over 60 years was 160 mg/L compared with a mean of 191 mg/L for those under 60 years.

Table II. Concentrations of caffeine determined in postmortem blood in poisoning deaths in relation to age and gender of the deceased

Gender	N (%)	Age (years) Mean ± SD	Blood–caffeine, mg/L Mean ± SD (median) range
Males	20 (39)	42 ± 17.2	183 ± 118 (162) 47–567
Females	31 (61)[a]	37 ± 18.3[b]	190 ± 82 (182) 33–400[c]
Both sexes	51 (100)	39 ± 17.8	187 ± 96 (180) 33–567

[a]No significant difference in proportion of males to females; chi-squared = 2.31, $P = 0.128$.

[b]No significant difference in mean age of men and women by Student's t-test ($t = 0.811$, $P = 0.42$).

[c]No significant gender difference in median concentration of caffeine in blood by non-parametric Mann–Whitney U-test ($z = 1.187$, $P = 0.235$).

Caffeine in central and peripheral blood

In 25 of the caffeine-related deaths, the drug was determined in femoral blood whereas in 19 cases cardiac blood was collected for toxicological analysis. In the remaining seven cases, the source of the autopsy blood was not specified in the published articles. One study analyzed caffeine in both cardiac and femoral blood and the results were 47 vs 49 mg/L, 180 vs 220 mg/L, 80 vs 74 mg/L and 300 vs 320 mg/L, respectively, which shows fairly close agreement and speaks against an appreciable postmortem redistribution (PMR) of caffeine (13). The plasma/blood distribution ratios of caffeine are also close to unity (43).

Manner of death

Table III presents manner of death in relation to the victim's age and gender and concentration of caffeine in postmortem blood. Mean age of the victims was not significantly different for accidental, suicide and undetermined manners of death ($F = 0.856$, $P = 0.431$). The median concentrations of caffeine in blood was lowest for undetermined manner of death (113 mg/L) and this differed significantly from deaths classified as accidental (183 mg/L) and suicide (185 mg/L), according to a non-parametric Kruskal–Wallis test ($P = 0.023$). Most of the caffeine-related deaths ($N = 26$ or 51%) were reported as being the result of a suicide attempt.

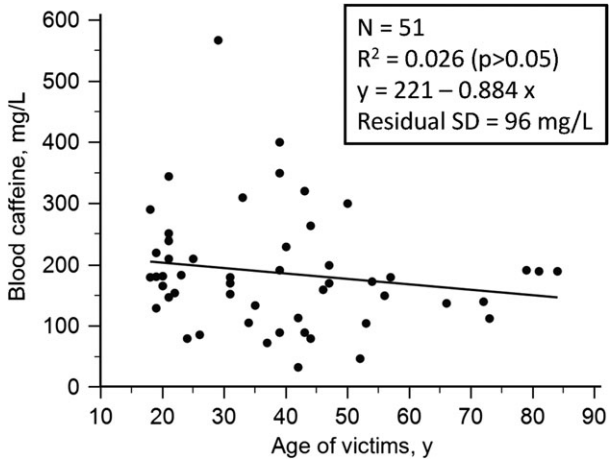

Figure 1. Lack of correlation between the concentrations of caffeine in postmortem blood and age of the deceased in 51 poisoning deaths.

Table III. Concentrations of caffeine in postmortem blood in relation to manner of death according to medical examiner reports when the cause of death was considered drug overdose (poisoning)

Manner of death	N (%)	Gender M/F	Age (years) mean ± SD	Blood–caffeine, mg/L Mean ± SD (median) range
Suicide	26 (51)	9/17	38 ± 21.2	203 ± 78 (185) 80–400
Undetermined	17 (33)	6/11	43 ± 12.5	137 ± 73 (113) 33–300[a]
Accidental	8 (16)	5/3	34 ± 15.3[b]	240 ± 147 (183) 134–567
All deaths	51 (100)	20/31	39 ± 17.8	187 ± 96 (180) 33–567

[a]Median blood–caffeine concentration was significantly lower for undetermined manner of death compared with accidental death and suicide, according to non-parametric Kruskal–Wallis test, $P = 0.023$.

[b]No differences between mean age in relation to manner of death by one-way ANOVA ($F = 0.856$, $P = 0.431$).

Co-ingested drugs

In the 51 poisoning deaths reviewed here, caffeine was the predominant psychoactive substance identified in autopsy blood samples. However, many of the victims had also used other drugs, such as ethanol, paracetamol (acetaminophen), acetylsalicylic acid, ephedrine, antidepressants and/or antipsychotics. However, the concentrations of these other substances were mostly in the therapeutic range, which suggests that they were incidental findings (44). Some over-the-counter medicines contain caffeine in combination with an analgesic or antipyretic drug, which explains the presence of these substances in autopsy blood samples.

In a case series of caffeine intoxication deaths ($N = 20$), caffeine was the only drug identified in five cases at a mean concentration of 188 mg/L (24). This compares with a mean of 158 mg/L in 15 cases when other drugs, in addition to caffeine, were identified in autopsy blood. Ethanol was present in five cases at concentrations ranging from 0.02 to 0.17 g%. In other victims, salicylic acid, acetaminophen and/or ephedrine were identified in blood samples, and these substances were probably combined with caffeine in a pharmaceutical product. Other drugs used by the victims of caffeine poisoning included antidepressants (e.g., citalopram/escitalopram), sleep-aids (zolpidem or zopiclone), antipsychotics (mirtazapine, olanzapine) and benzodiazepines (oxazepam or flunitrazepam).

Concentrations of caffeine in postmortem blood

Figure 2 presents a relative frequency distribution of caffeine concentrations in blood in 51 poisoning deaths. The distribution is slightly skewed to the right as is often observed for drugs encountered in overdose deaths. The mean (±SD), median and lowest and highest concentrations of caffeine in postmortem blood were 187 ± 96 , 180, and 33–567 mg/L, respectively.

Figure 3 is a cumulative frequency distribution plot, which makes it easier to visualize the percentage of cases above certain threshold concentrations of caffeine in blood. The median value (50%) is indicated on the plot (180 mg/L) and the 10th and 90th percentile concentrations were 84 and 314 mg/L, respectively.

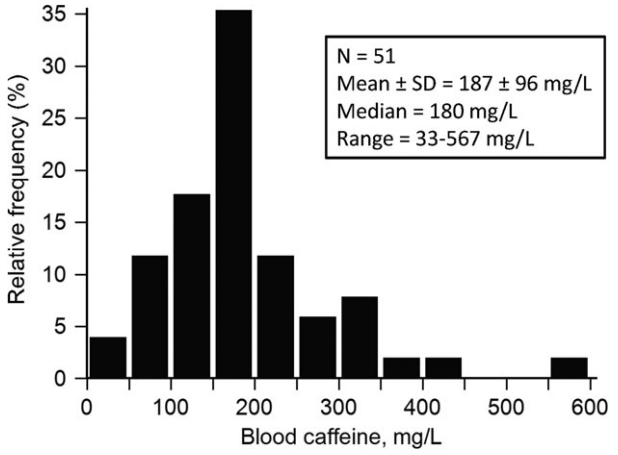

Figure 2. Relative frequency distribution of caffeine concentrations in autopsy blood from 51 victims of poisoning (overdose) deaths.

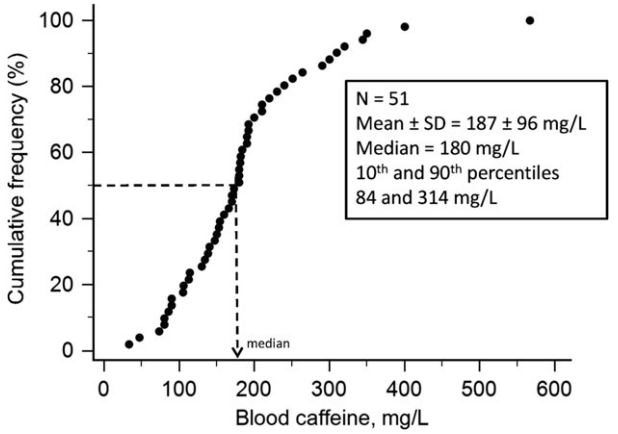

Figure 3. Cumulative frequency distribution of the concentrations of caffeine in autopsy blood from 51 poisoning (overdose) deaths.

Discussion and Conclusion

Musgrave *et al.* (45) recently published a paper entitled "Caffeine toxicity in forensic practice: possible effects and under-appreciated sources" although their review did not provide much information about the blood concentrations of caffeine in poisoning deaths. The present article presents descriptive statistics for the concentrations of caffeine in 51 such deaths when caffeine was taken as tablets or in powder form, although there might have been minor contributions from drinking caffeinated beverages before death.

In a review of caffeine-related deaths in Tokyo between 2008 and 2013 when concentrations in blood were above 15 mg/L ($N = 22$ cases) most victims were female (59%) aged between 20 and 49 years ($N = 14$) and 64–73% of the deceased had a history of some psychiatric disorder, mainly depression (25). The manner of death was certified as undetermined in 11 cases, accidental in 7 cases and suicide in 2 cases. In 16 deaths attributed to caffeine intoxication, the mean concentration in cardiac blood was 179 mg/L, which compared with a mean of 39 mg/L when death was from other causes ($N = 6$ cases). The mean concentration of caffeine in cardiac blood from the Japanese study of 179 mg/L is in good agreement with a mean of 187 mg/L in the present compilation of 51 caffeine intoxication deaths.

In a listing of the drugs identified in blood in ~25,000 forensic autopsies in Sweden representing all causes of death, we found that caffeine was in 19th position in terms of prevalence (46). The use of a high analytical cut-off concentration of 10 mg/L ensures that cases with caffeine present in blood from drinking caffeinated beverages are not included. The mean, (median) and upper 97.5th percentile concentration of caffeine in femoral blood were 22 mg/L, (14 mg/L) and 155 mg/L, respectively ($N = 268$ cases). This makes it clear that some of the deaths represent overdosing and intoxication from caffeine toxicity.

A retrospective study of 22,125 forensic autopsies reported in Finland found mean, median and upper 97.5th percentile concentrations of caffeine of 4, 3 and 13 mg/L, respectively (47). These concentrations are much lower than those form Sweden, but this Finnish Laboratory used an analytical cut-off concentration of 1–3 mg/L. The results therefore reflect blood–caffeine concentrations resulting from normal consumption of caffeinated beverages. Taking a median concentration of caffeine from the Finnish study as 3 mg/L, when this is compared with a median of 180 mg/L in the 51 intoxication deaths reported here, one arrives at a therapeutic index for caffeine in humans of 60 (180/3 = 60).

Various compilations of therapeutic, toxic and fatal concentrations of drugs are available in the literature and these are useful to

consider when drug overdose deaths are investigated (48). In one such compilation, a caffeine concentration in blood below 10 mg/L was considered harmless (49). Concentrations in blood between 15 and 20 mg/L were considered elevated, but still not toxic or a danger to health, whereas levels between 80 and 180 mg/L were associated with caffeine-related fatalities (49). Another compilation of caffeine-related deaths reported that a concentration >100 mg/L in blood should be interpreted as a poisoning or intoxication death (50).

The median concentrations of caffeine in 51 caffeine poisoning deaths were 180 mg/L, and the 10th and 90th percentile concentrations were 84 and 314 mg/L, respectively (Figure 3). Victims with a relatively low concentration of caffeine in blood might have survived for several hours or received hospital treatment, including hemodialysis. During the survival time, the concentrations of caffeine in blood decrease through metabolism ($t_{1/2}$ = 3–7 h). Furthermore, the co-ingestion of other drugs might have enhanced the toxicity of caffeine, although for the 51 deaths reviewed here caffeine was the predominant psychoactive substance in blood. Another factor to consider is the presence of any natural disease, such as cardiovascular and respiratory problems in the elderly. These conditions might make elderly individuals more susceptible to caffeine toxicity, although the mean concentration in blood from people over 60 years (N = 6) was 160 mg/L compared with a mean of 191 mg/L for those younger than 60 years (N = 45).

The propensity of caffeine to redistribute between blood and tissue compartments after death has not been extensively studied by direct comparison of central and peripheral blood concentrations. The four cases reported in this paper do not support a significant PMR (13). Caffeine distributes into the total body water compartment and has a volume of distribution close to 0.70 L/kg on average (31), so PMR is not expected to represent a serious problem for interpreting blood concentrations of this drug.

In a 2012 review, Han *et al.* (43) reported a central-to-peripheral distribution ratio of 1.1:1 (N = 1) for caffeine. In a report from Canada, Dalpe-Scott *et al.* (51) reported a mean heart/femoral blood concentration ratio of 1.2:1 (range 1.0–1.4) in three cases. The concentrations of caffeine in femoral blood when bodies were admitted to the mortuary (median 4.1 mg/L) were slightly higher than when an autopsy was performed 59 h later (median 3.6 mg/L). This decrease in concentration was statistically significant although these caffeine concentrations are very low and not at all in the toxic range (52).

Although it is generally considered controversial to convert a postmortem drug concentration into the amount of substance in the body at the time of death, especially for drugs with a propensity for PMR, an exception might be made for caffeine until more information becomes available. For a person with body weight of 70 kg and 180 mg/L caffeine in blood, a simple calculation shows that there are 8.8 g caffeine absorbed and distributed in all body fluids and tissues (0.180 g/L × 0.7 L/kg × 70 kg). If one caffeine tablet contains 100 mg then a 70 kg person would need to swallow ~88 tablets to account for a postmortem blood concentration of 180 mg/L. This large number of tablets is supported by the death of a 21-year-old-woman who reported taking 100 caffeine tablets (10 g) in a suicide attempt, but then had second thoughts and called the emergency services (24). The woman died after 10 days of intensive care treatment, including hemodialysis.

The manner of death whether accident, suicide or undetermined was ascertained by medical examiner and/or forensic pathologists who did an autopsy and after considering all available information in the case. However, there may well be differences in how the manner of death is certified in different countries and also between medical examiner offices in the same country (53). This difference is particularly evident when deciding between accidental as opposed to undetermined manner of death, whereas suicide is more unequivocal, for example, if a farewell note is discovered or the deceased suffered from depression or had attempted suicide on a previous occasion (54).

In conclusion, this review of the literature identified 51 caffeine-related poisoning deaths with a mean concentration in blood (±SD) of 187 ± 96 mg/L (median 180 mg/L) and 10th and 90th percentile concentrations of 84 and 314 mg/L, respectively. Most of the victims were females (61%) and the manner of death was suicide in 51% of cases. The average age of the deceased was 39 ± 17.8 years (range 18–84 years), although there was no correlation between blood–caffeine concentration and victim's age.

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