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A Case Report of Fatal Caffeine Intoxication: Nonspecific Postmortem Distribution

تقرير حالة عن التسمم القاتل بالكافيين: توزيع غير محدد بعد الوفاة

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Abstract

Caffeine, a mild central nervous system (CNS) stimulant present in coffee beans, cocoa beans, and tea leaves, can pose a threat in significant quantities, leading to severe health complications like arrhythmia, tachycardia vomiting, convulsions, coma, and, in extreme cases, death.

We present a case involving the tragic demise of a young woman who took her own life by consuming a sleepiness-preventing medication purchased online, containing caffeine. The autopsy revealed pulmonary edema, congestion, and cutaneous emphysema. The stomach contents included a dark-brown viscous fluid with remnants of tablets and food. Toxicological analysis indicated elevated caffeine levels in various body tissues: femoral blood (195 mg/L), brain (115 μg/g), lung (293 mg/g), liver (202 mg/g), spleen (692 mg/g), kidney (288 μg/g), gall bladder (bile juice) (1500 μg/g), skeletal muscle (163 μg/g), small intestine (236 μg/g), and myocardial muscle (682 μg/g). Due to the presence of caffeine tablets in the stomach, the concentration was exceptionally high and therefore not quantified. The highest concentration of caffeine was found in the bile (1500 μg/g). The gas chromatography mass spectrometry (GC/MS) method used was validated according to the GTFCh guidelines. This case emphasizes

Keywords: Forensic sciences, Caffeine, Overdose, Suicidal poisoning, Distribution, GC/MS.

المستخلص

الكافيين منبه معتدل للجهاز العصبي المركزي (CNS) موجود في حبوب البن، وحبوب الكاكاو، وأوراق الشاي، ويمكن أن يشكل تهديدًا بكميات كبيرة، مما يؤدي إلى مضاعفات صحية خطيرة مثل: اضطراب ضربات القلب، وتسارع دقات القلب، والتقيؤ، والتشنجات، والغيبوبة، وفي الحالات الشديدة. يؤدي للموت.

نعرض حالة تتعلق بالوفاة المأساوية لامرأة شابة انتحرت عن طريق تناول دواء لمنع النعاس تم شراؤه عبر الإنترنت، ويحتوي على مادة الكافيين. وكشف تشريح الجثة عن وذمة رئوية، واحتقان، وانتفاخ الرئة. وتضمنت محتويات المعدة سائلاً لزجاً بني داكناً مع بقايا أقراص وطعام. أشار تحليل السمية إلى ارتفاع مستويات الكافيين في أنسجة الجسم المختلفة: دم الفخذ (195 ملغم/لتر)، الدماغ (115 ميكروغرام/غرام)، الرئة (293 ملغم/غرام)، الكبد (202 ملغم/غرام)، الطحال (692 ملغم/غرام) والكلى (288 ميكروجرام/جم)، والمرارة (العصارة الصفراوية) (1500 ميكروجرام/جم)، والعضلات الهيكلية (163 ميكروجرام/جم)، والأمعاء الدقيقة (236 ميكروجرام/جم)، وعضلة القلب (682 ميكروجرام/جم). ونظرًا لوجود أقراص الكافيين في المعدة، كان التركيز مرتفعًا بشكل استثنائي، وبالتالي لم يتم تحديد كميته. تم العثور على أعلى تركيز للكافيين في المرارة (1500 ميكروجرام/جرام). تم التحقق من صحة طريقة قياس الطيف الكتلي للغاز اللوني (GC/MS) المستخدمة وفقًا لإرشادات (GTFCh).

الكلمات المفتاحية: علوم الأدلة الجنائية، الكافيين، الجرعة الزائدة، التسمم الانتحاري، التوزيع، جهاز GC/MS.

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the importance of caution and highlights the study's recommendation to address the toxicity risks associated with substances containing high caffeine concentrations. The suggestion is to include caffeine concentration assessments in routine forensic toxicological tests for all cases. In this case the cause of death was determined to be caffeine intoxication, with no trace of ethyl alcohol, drugs, pesticides hydrocarbons, or organic solvents detected in the body samples.

وتؤكد هذه الحالة على أهمية الحذر من مادة الكافيين وتسلط الضوء على توصية الدراسة لمعالجة مخاطر السمية المرتبطة بالمواد التي تحتوي على تركيزات عالية من الكافيين. وتقترح أن يتم إدراج تقييمات تركيز الكافيين في اختبارات السموم الشرعية الروتينية لجميع الحالات. في هذه الدراسة تم تحديد سبب الوفاة على أنه تسمم بالكافيين، مع عدم وجود أثر للكحول الإيثيلي أو المخدرات أو المبيدات الحشرية الهيدروكربونية أو المذيبات العضوية في عينات الجسم.

1. Introduction

Caffeine (C8H10N4O2) is an alkaloid and psychostimulant derived from plants. It naturally occurs in tea leaves, coffee, cocoa beans, and kola nuts. Routine detection of caffeine, along with theophylline, theobromine, and paraxanthine, in toxicological samples is attributed to dietary exposure. Functioning as a mild central nervous system stimulant, caffeine is inherent in coffee beans, cocoa beans, and tea leaves. However, when consumed in large quantities, it can lead to severe toxicity, manifesting as arrhythmia, tachycardia, vomiting, convulsions, coma, and even death. The reported caffeine content in an average cup of coffee or tea in the United States ranges from 40 to 150 mg [1], with specialty coffees potentially containing higher doses [2]. Upon oral administration, caffeine undergoes rapid absorption. In a study involving 36 subjects receiving a single 130 mg oral dose, peak plasma concentrations ranged from 2.5 to 6.8 mg/L, with a mean value of 4.0 mg/L within 20–40 minutes [3]. Notably, around 90% of the caffeine in a cup of coffee is absorbed from the stomach within the first 20 minutes, reaching peak plasma concentrations approximately 40–60 minutes later. Reported plasma/blood ratios stand at 0.93, and the volume of distribution is estimated to be 0.5 L/kg [4]. Understanding the pharmacokinetics of caffeine is crucial for comprehending its effects on the human body and its relevance in toxicology.

Caffeine, a widely embraced stimulant known for its role in boosting cognitive alertness, is commonly found in a variety of natural foods and over-the-counter products. While it is frequently used to enhance mental focus, recent attention has shifted to the potential toxicity associated with caffeine, particularly in tablets and energy drinks [5]. Despite this concern, instances of caffeine overdose remain rare [6]. Furthermore, there is a lack of comprehensive case reports elucidating the toxicodynamic of caffeine levels within the human body. The need for a better understanding of how caffeine affects the body, especially in the context of potential toxicity, underscores the importance of continued research to ensure the safe consumption of this widely used stimulant.

This case report delves into a fatal incident of caffeine poisoning, examining a patient's condition through a comprehensive analysis of caffeine in different biological matrices. The perilous state resulted from the consumption of over-the-counter supplements, designed to alleviate fatigue, containing 100–200 mg of caffeine per tablet. Notably, various prescription drug combinations incorporate doses ranging from 32 to 200 mg. The alarming nature of this case highlights the crucial needs for awareness regarding the potential dangers associated with both non-prescription and prescription sources of caffeine. This emphasizes the importance of exercising caution in their usage to prevent life-threatening complications.

2. Case report

The Decedent was a 19 years old European female; the decedent had been noted to be missing

for one week prior to the discovery of her body by the Dubai Police. The Dubai Police crime scene team ultimately located the daughter's whereabouts, unveiling a disconcerting scene in their report. The room bore signs of chaos, with the slightly decomposed body of the young girl discovered amidst brownish spots on the bed and floor—later identified as diarrheal stool. Notably, a partially consumed bottle labeled as Muscletech® "100% caffeine" was found at the scene, and whitish foaming residues adorned the lips and chin of the deceased.

The autopsy yielded limited significant findings, aside from a grayish fluid in the stomach with a nondescript odor. However, a comprehensive toxicological analysis of post-mortem specimens revealed elevated caffeine concentrations in the blood, as well as in all examined tissues and body fluids. Subsequent investigations on postmortem materials confirmed uniformly high levels of caffeine distribution throughout the body.

3. Material and Methods

3.1. Materials

Caffeine (5 gm) and Cocaine-D3 (1 mg/mL) reference standards were purchase from Sigma-Aldrich (Germany) and Cerilliant (Germany) respectively. Certified drug free urine and whole blood were purchased from UTAK (United States of America). De-Tox A tubes were purchased from Clearsynthetic Life Science (United States of America). Additionally, all other chemicals utilized were of HPLC reagent grade unless explicitly specified.

3. 2. Stock solutions

A freshly prepared caffeine stock solution was made in methanol at a concentration of 1 mg/mL and stored at 4 ºC. For calibration and method validation, caffeine stock solution was diluted in methanol to create a working standard solution with concentrations of 100 μg/mL and 10 μg/mL.

3.3. Internal standards

The working standard solution of 100 μg/mLwas prepared by diluting the internal standard Cocaine–D3 (1 mg/mL) with methanol.

3.4. Instrumentation

Caffeine analysis was done using a gas chromatography/mass spectrometry (GC/MS) system manufactured by Hewlett Packard: GC 6890 MSD 5973, featuring a Hewlett Packard auto-injector with an autosampler. The DB-5 MS column, measuring 30 meters in length with an inner diameter of 0.25 mm and a film thickness of 0.25 μm. Helium was employed as the carrier gas at a flow rate of 1mL/min. The injector operated in splitless mode, with a 2 μl injection volume, 50 mL/min purge flow, and a 2 mL/min purge time. The Gas Saver was activated with a flow of 20 mL/min and a time of 2.0 minutes. The injector temperature was set at 280 °C, transfer line temperature at 280 °C, and ionization source temperature at 230 °C. For caffeine detection, the temperature program initiated at 70 °C for 0 minutes, followed by a ramp of 12 °C/min up to 280 °C, maintaining a final hold time of 3 minutes (total run time: 20.5 minutes). Mass spectrometric analysis in positive electron impact ionization mode (EI) at 70 eV covered a scan range of 40 to 550 amu. Quantitative measurement occurred in selected ion monitoring mode, focusing on m/z values 194 (Quantifier), 109, 67 (Qualifier) for caffeine and 306 (Quantifier), 185 (Qualifier) for cocaine-D3 (Figure 1) with a retention time of 12.925 minutes and 16.057 for caffeine and cocaine-D3 (Figure 2) respectively. Full mass spectrum and selected ion monitoring (SIM) chromatogram for caffeine and cocaine-D3 shown in Figure 1 and Figure 2 respectively.

3.5. Toxicological examination

Blood samples underwent screening for commonly abused drugs Table 1, using the Randox Multistat

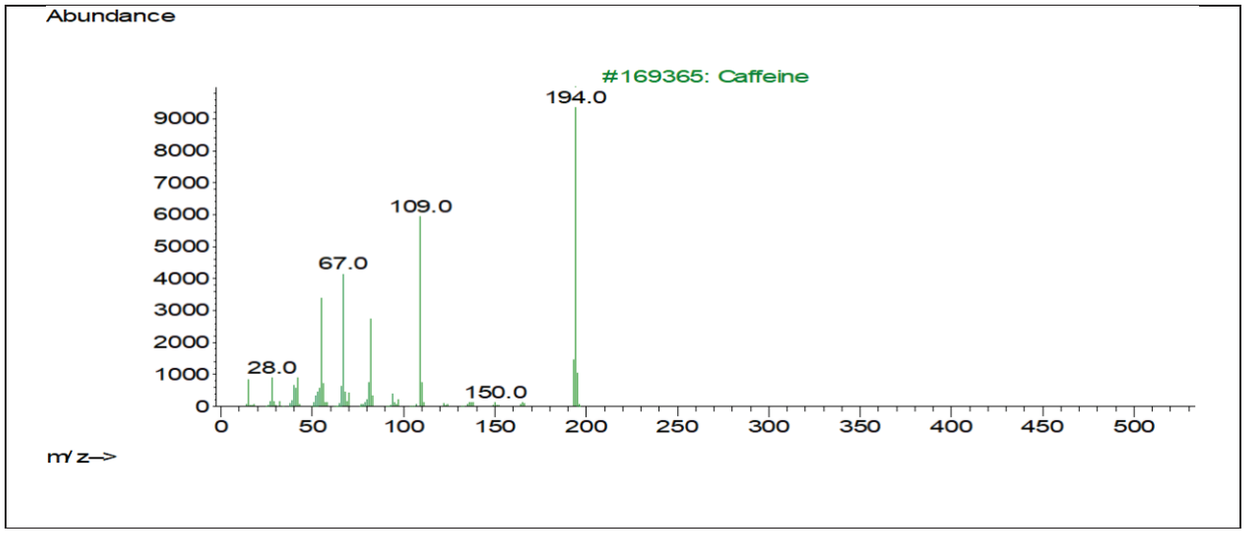

Figure 1 (a). *Showing mass spectrum obtained for Caffeine.*

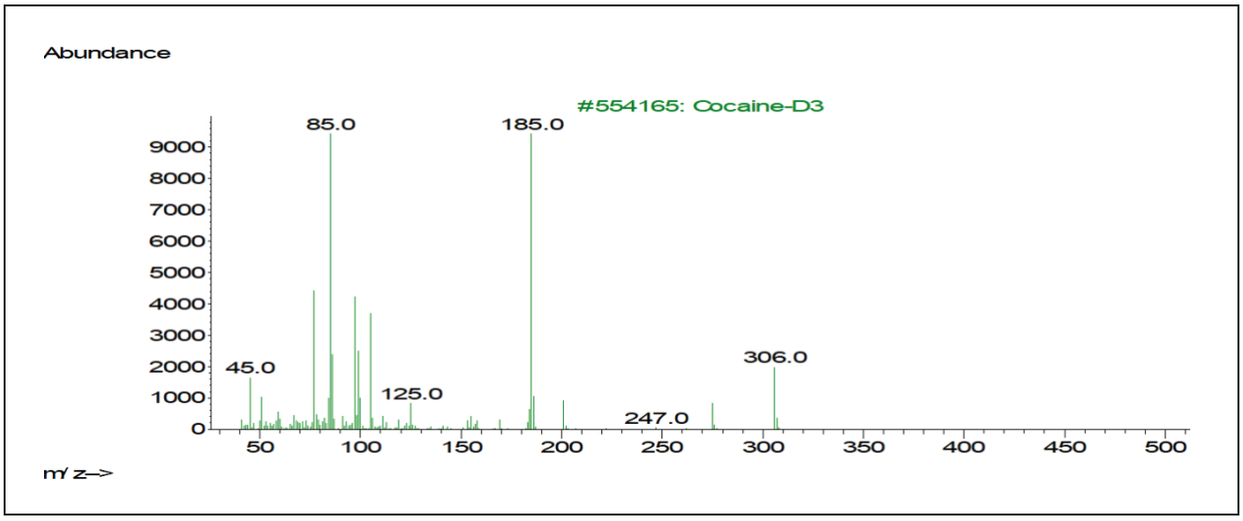

Figure 1 (b). *Showing mass spectrum obtained for Codeine-D3.*

Biochip Array Technology immune assay technique, yielding negative results. No traces of ethyl alcohol or other organic volatile compounds (Methanol, acetone and isopropanol) were detected [7].

3.5. Sample preparation

A portion of the case samples, comprising 1 mL of blood, gastric contents transfer to the 15 mL screw cap tube, no urine sample was available to collect during autopsy. One gram of each tissue sample (brain, myocardial muscle, liver, lung, skeletal muscle, kidney, and gall bladder (bile)), was diluted with 1:2 w/v (tissue and aqueous 1% sodium fluoride) and then placed in stomacher bad, which was then place in stomacher apparatus and underwent homogenization for 5 minutes. An aliquot of 50 mg each homogenized samples were subsequently moved to individually labeled 15 mL screw cap tubes. To the all above sample tubes, 1 mL of deionized water was added, followed by the addition of 10 μL of 100 μg/mLcocaine-D3 as an internal standard (IS). The mixture was vortexed for 30 s

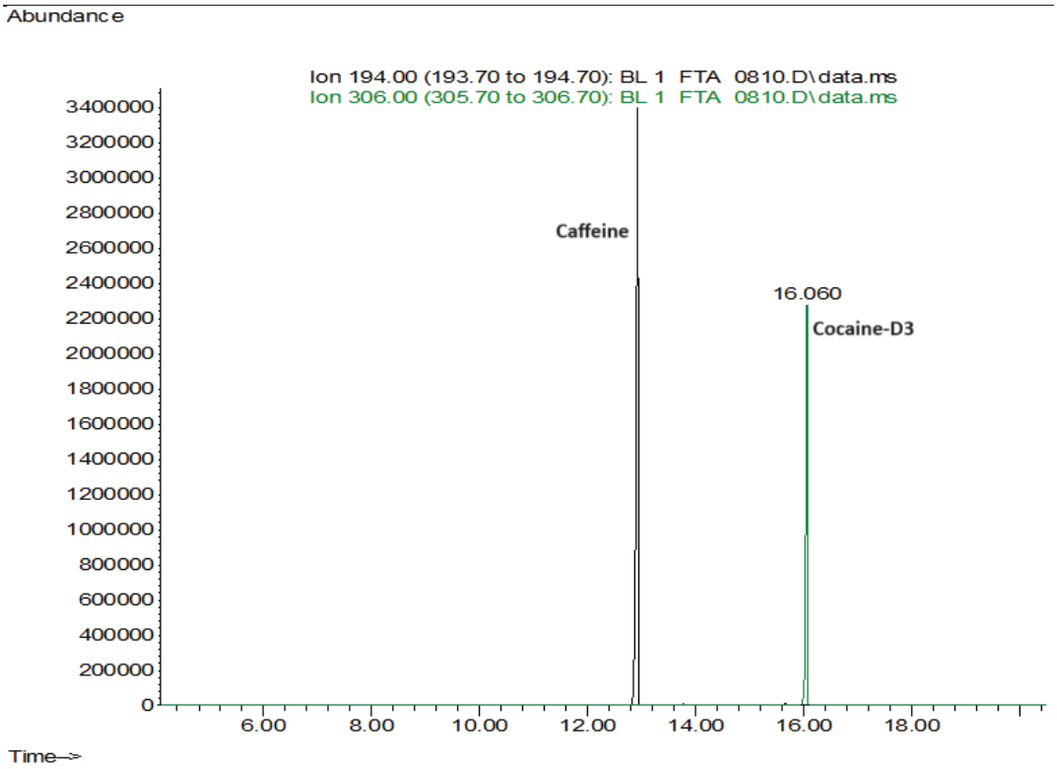

Figure 2 - *Selected Ion Monitoring (SIM) Chromatogram obtained for Femoral blood.*

Table 1- Showing the panel of abused drug screened in blood sample by Randox Multistat.

S. No	Drug Name	S. No	Drug Name
1	PVP (Flakka)	11	Methamphetamine
2	Amphetamine	12	Opiate
3	Barbutirates	13	Oxycodone
4	Benzodiazepines	14	Phencyclidine (PCP)
5	Benzoylecgonine	15	Pregabalin
6	Buprenorphine	16	Synthetic cannabinoids (AB-CHIMINACA)
7	Cannabinoids	17	Synthetic cannabinoids (AB-PINACA)
8	Ethyl Glucuronide (EtG)	18	Tramadol
9	Fentanyl	19	Tricyclic Antidepressants (TCA)
10	Methadone	20	6-MAM

and then transferred to De-Tox A extraction tubes. These extraction tubes underwent rotational agitation in a rotoshaker (Stuart) for 10 min and subsequently centrifuged at 4000 rpm for 5 min at 4 °C to prevent emulsion formation. The resulting organic layer was then transferred to glass vials and evaporated to dryness using a gentle stream of nitrogen. The dry residue was reconstituted in 50 μl of ethyl acetate, and 2 μL of the reconstituted sample analyzed by GC/MS.

Validation studies and the preparation of calibration curves involved the use of negative blood from UTAK. Additionally, tissues such as brain, myocardial muscle, liver, lung, skeletal muscle, kidney, and gall bladder (bile) were obtained from various negative postmortem cases for matrix matching. These tissues were spiked with varying concentrations of caffeine within the range of 50 ng/mL to 15,000 ng/mL, along with 10 μL of 100 μg/mL cocaine-D3 (internal standard). The standard spiked matrices were processed in a manner similar to the aforementioned case samples.

4. Results

The toxicology findings in this case revealed a caffeine concentration of 195 mg/L in the femoral blood, with the source traced back to a partially consumed bottle labeled as Muscletech® "100% caffeine" found at the scene. Table 2 provides a summary of the post-mortem caffeine concentrations in the samples that were tested. The methodology employed was validated in accordance to the GTFCh guidelines, Table 3 [8].

Fatal incidents among adults are rare, typically occurring after doses ranging from 5 to 50 grams, with reported recovery even after a 30-gram ingestion [1]. Typically, toxic reactions leading to fatality have been linked with blood concentrations exceeding 15 mg/L and fatal reactions occur at levels surpassing 80 mg/L [4, 5, 6].

Study of distribution of caffeine was important to observe in case of suspected fatality due to its overdose. Postmortem concentrations of the caffeine among several organs to be compare with the previous studies [4, 9] which describes the distribution of caffeine in several organs. Our results were shown as acceptable compare to the published studies specially in the case of suicide by ingestion of high concentration of caffeine in any oral forms.

Fatal caffeine overdose remains relatively unreported in the scientific literature; however, we present first incidence in UAE region where we were able to get examined different postmortem specimens for detection of caffeine. In these instances, death was attributed to caffeine intoxication, and the manner of death was ruled as suicide. Routine toxicological screening detected neither blood alcohol nor any drugs in the examined tissues.

Table 2- Showing the concentration of Caffeine in postmortem specimens.

S. No	Sample matrices	Caffeine Concentration (mg/L or μg/g)
1	Femoral Blood	195
2	Brain	115
3	Lung	293
4	Liver	202
5	Spleen	692
6	Kidney	288
7	Gall bladder (bile)	1500
8	Skeletal muscle femoral	163
9	Myocardial muscle	682
10	Small intestine	236
11	Stomach content	Extreme high detected not quantified

Table 3- Showing the validation parameters for Caffeine.

S. No	Parameters	Value
1	Linearity range	200 – 10000 ng/ml
2	Regression (R^2)	0.996
3	Limit of detection (LOD)	100 ng/ml
4	Limit of quantitation (LOQ)	200 ng/ml
5	Repeatability	8.46 (% RSD)
6	Reproducibility	10.87 (% RSD)
7	Relative Recovery	>90 %

5. Discussion

Caffeine is a common component available on internet and sold as performance enhancing dietary/ excercise suppliments, also available as over the counter medications, and prescription drug combinations, with doses ranging typically ranging from 32 to 200 mg. A standard cup of coffee is estimated to contain around 100 mg of caffeine [1, 10, 16, 17]. Adverse reactions, including toxic and fatal outcomes, have been linked to blood concentrations surpassing 15 and 80 mg/L, respectively [2, 10, 11].

Upon oral administration caffeine rapidly undergoes absorption, with in 20 mins 90% of the caffeine is absorbed rapidly through gastrointestinal tract [12]. In this case study caffeine concentration in small intestine was 236 μg/g detected, where as in stomach content caffeine concentration could not be determined due to extreme concentrations. The average half-life of the caffeine is 2 – 12 hrs [13-16]. Upon administration peak plasma concentration reached within 30-120 mins [17]. Due to caffeine lipophilic moiety and limited plasma protein binding capacity, it will enter all the tissues through call membrane and also enter intercellular tissue water [17-19]. Due to its lipophilic moiety it can cross the blood brain barrier which is also confirmed by detection of caffeine I brain tissues (115 μg/g) in present case study. After absorption through small intestine caffeine will undergoes first phase metabolism in liver. In case of high dose administration, the metabolism will be saturated [20-22]. High concentrations of caffeine detected in spleen (692 μg/g) and bile (1500 μg/g) compare to the earlier reported fatal case [23], whereas liver concentration was around 202 μg/g. Detection of high concentration of caffeine in these specimens could be due to enterohepatic circulation. And also high concentration of caffeine in myocardial muscle (682 μg/g) [24] will suggest the possible cause of death due to ventricular fibrillation induced by caffeine [25]. Other postmortem specimens like kidney (288 μg/g), lung (293 μg/g) and skeletal muscle from femoral region (293 μg/g) shows varying concentration of caffeine.

In summary, our study provides a comprehensive analysis to exclude the possibility of fatal intoxication due to other drugs and substances and to established a correlation between tragic demise of young woman and caffeine intoxication linked to the consumption of performance enhancing/sleep-preventing medication. We advocate for increased awareness of the potential toxicity associated with the ingestion of substances containing elevated caffeine concentrations. Emphasizing the importance of recognizing this risk, we propose the integration of peripheral blood caffeine cut-off concentration of 80 mg/L (26) and above to be reported in case of single drug (caffeine) intoxication is suspected. Additional testing on hair is recommended with a

caffeine concentration cut-off value of 5.5 ng/mg to distinguish between normal consumption or abuse as suggested in a study [27]. This recommendation aims to enhance forensic investigations by providing a more thorough understanding of the toxicological profile in instances of self-harm related to caffeine overdose. By incorporating such evaluations into standard protocols, we strive to contribute to the prevention of similar tragedies and promote a more comprehensive approach to forensic examinations in cases involving toxic substances.

Conflict of interest

The authors declare no conflicts of interest.

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Author's contribution

F.A. Tarbah, Design, supervise the experiment, interpretation of results and manuscript preparation.

H.S. Saeed, Carried out the experiment.

M.J. Alfayumi, Carried out the experiment.

H.I Belshalat, Carried out the experiment.

N.A. Ansari, Carried out the experiment and interpretation of results.

H.M. Sherief, Performed the autopsy and collected the samples.

M.M. Habiballah, Performed the autopsy and collected the samples

F. AL Teneiji, Carried out the experiment, analysis of the sample on GCMS.

E. Alabdooli, Carried out the experiment, analysis of the sample on GCMS.

A. Sankar, Analysis of the sample on GCMS.

Y. Elsayed, Technical review and manuscript preparation.

M. Idris, Technical review and manuscript preparation.

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