Original Article

Serum potassium level as a biomarker for acute caffeine poisoning

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Aim: Acute caffeine poisoning presents with hypokalemia, although a relationship between potassium levels and blood concentrations of caffeine has not been established. A correlation between serum potassium level and blood caffeine concentration could establish serum potassium as a simple marker to assess caffeine toxicity in patients with acute toxicity. We investigated whether serum potassium, a symptom of acute caffeine poisoning, could be a parameter correlated with blood caffeine levels.

Methods: We enrolled 85 patients treated for acute caffeine poisoning between January 2012 and March 2019 with blood caffeine levels measured after an overdose of a caffeine-containing over-the-counter drug and for whom serum potassium levels were available. We examined the correlation between serum potassium and blood caffeine concentration. A receiver operating characteristic curve was created with serum potassium values to stratify participants into two groups by blood caffeine concentrations: <20 or ≥20 mg/L (toxic dose) and <80 or ≥80 mg/L (lethal dose). The lethal cut-off value was calculated.

Results: The correlation coefficient between serum potassium level and blood caffeine concentration was −0.612 (R^2 = 0.374), indicating a negative correlation. The areas under the curve at blood caffeine concentrations of 20 mg/L (toxic dose) and 80 mg/L (lethal dose) and serum potassium levels were 0.716 and 0.888 (sensitivity, 0.829 and 0.919; specificity, 0.568 and 0.818; cut-off, 3.3 mEq/L and 2.9 mEq/L), respectively.

Conclusion: Serum potassium levels are associated with blood caffeine concentrations; K^+ of 3.3 mEq/L and 2.9 mEq/L indicate acute caffeine poisoning in the toxic and lethal dose, respectively.

Key words: Acute caffeine poisoning, blood caffeine concentration, hypokalemia, lethal dose, serum potassium

INTRODUCTION

IN RECENT YEARS, severe cases of acute caffeine poisoning, and even deaths resulting from acute caffeine poisoning, have been reported worldwide and various countries have issued warnings concerning caffeine overdose.[1–3] Reported symptoms of acute caffeine poisoning include gastrointestinal symptoms such as nausea and vomiting, central nervous system symptoms such as convulsions and impaired consciousness, and cardiovascular symptoms such as fatal arrhythmia and shock.[4] Acute caffeine poisoning causes hypokalemia; however, the relationship between levels of serum potassium and blood caffeine is unknown. Currently, facilities that can measure blood caffeine levels are limited, and it is difficult to carry out treatments based on blood levels in real time. The identification of a correlation between serum potassium and blood caffeine concentration could facilitate the establishment of a standard, accessible parameter for the monitoring of caffeine poisoning in patients who present to the emergency department. In this study, the correlation between blood caffeine concentrations and serum potassium levels in acute caffeine intoxication was determined, and the cut-off values for serum potassium levels in the intoxication and lethal areas were calculated based on the correlation.

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METHODS

Study design

FROM JANUARY 2012 to March 2019, 386 patients were hospitalized to our Trauma and Emergency

Center with overdoses of over-the-counter caffeine-containing drugs. When each patient came to the hospital, we took blood samples with other blood tests. After excluding patients who had taken multiple drugs prescribed at the hospital, such as benzodiazepines and antipsychotics, we included 85 patients. Their clinical parameters were confirmed retrospectively. Details of patient characteristics and their clinical course are presented in Table 1.

Table 1. Baseline characteristics and clinical course of study participants with acute caffeine poisoning (n = 85)

Characteristic	N = 85
Men	19 (22.4)
Women	66 (77.6)
Age, years	24 (19–33)
Alcohol intake	17 (20.0)
Estimated caffeine intake	
Total concentration, mg	1365 (800.0–2387.5)
Concentration by body weight, mg/kg	23.7 (13.9–55.5)
Time from ingestion, min	215 (106.5–419.5)
Symptoms	
Nausea	35 (41.2)
Headache	7 (8.2)
Fatigue	5 (5.9)
Palpitation	3 (3.5)
Convulsion	1 (1.2)
Vertigo	1 (1.2)
Vital signs at admission	
Glasgow Coma Scale score	15 (14–15)
Systolic blood pressure, mmHg	130 (110–138)
Pulse rate, b.p.m.	99 (87–114)
Respiratory rate, cycles/min	18 (16–24)
Blood test at admission	
Na, mEq/L	142 (140–143)
K, mEq/L	3.4 (3.0–3.4)
Cl, mEq/L	103 (101–106)
Creatinine, mg/dL	0.6 (0.53–0.81)
Blood urea nitrogen, mg/dL	10 (8–12)
Glucose, mg/dL	119 (102.8–151.5)
Lactate, mg/dL	27 (15–41)
Serum caffeine level, mg/L	20.5 (10.3–48.0)
Treatment	
Hemodialysis	7 (7.4)
Outcome	
In-hospital death	0 (0.0)
Hospital stay, days	3 (2–4)

Data are shown as n (%) or median (interquartile range).

Testing

Anticoagulant was not used for blood collection. Collected blood was centrifuged for 10 min at 403 × g. The serum sample was then frozen at −30°C and analyzed within 48 h. The drug determination was undertaken using liquid chromatography–tandem mass spectrometry (LC-MS/MS) after solid-phase extraction. Internal standards including 5 ng caffeine-d9 and acetaminophen-d4 were added to 0.02 mL of the serum sample. Subsequently, 0.8 mL distilled water was added to each sample. The samples were mixed well using a vortex mixer for 15 s and then each sample was applied to the conditioned solid-phase extraction cartridges by methanol and distilled water. The cartridges were then washed with distilled water and 5% methanol and dried under vacuum. The residual compounds were eluted with chloroform–methanol (9:1), and the eluate evaporated to dryness under a stream of nitrogen at room temperature. The dry residue was then dissolved in mobile phase and injected into the LC system.

Chromatographic separation was carried out on an InertSustain C18 HP 3 μm (3 mm × 100 mm) column at 40°C by using the Agilent (Santa Clara, CA, USA) 1200 LC system. Gradient conditions were used for chromatographic separation in which mobile phase A consisted of water with 0.1% acetic acid, and mobile phase B consisted of acetonitrile. Detection on electrospray ionization MS/MS was achieved using an Agilent 6410 Triple Quadrupole Mass Spectrometer by using the positive ionization mode, and the ions were monitored using the multiple reaction monitoring mode.

Statistical analysis

For the purposes of data analysis, we examined the following two points. We constructed a correlation diagram from the baseline serum potassium level at hospitalization and blood concentration of caffeine, and calculated the correlation coefficient in patients with acute caffeine poisoning. Generally, caffeine blood concentration of 20 mg/L is considered to be an addiction range,[5] so we stratified the study participants by blood caffeine concentrations of 20 mg/L or more (toxic level) and less than 20 mg/L, to create a receiver operating characteristic (ROC) curve based on serum levels of potassium; thereafter, we aimed to calculate the area under the curve (AUC) and a cut-off point for the toxicity range. In addition, caffeine blood concentration of 80 mg/L is considered to be lethal range,[6] so we classified participants based on lethal blood caffeine concentrations below or above 80 mg/L, and a ROC curve was created for these patient subgroups as well with the serum potassium values;

again, we aimed to calculate the AUC and a cut-off value for the lethal region based on serum potassium levels. The cut-off value was calculated using the Youden index.

All statistical analyses were undertaken using the IBM SPSS Statistics version 25 software program (Tokyo, Japan) (Spearman's rank correlation coefficient; $P < 0.05$).

RESULTS

FIGURE 1 SHOWS a scatterplot of the serum potassium level and blood caffeine concentration that indicates the association between the two parameters. However, a correlation coefficient of −0.612 (R^2 0.347) was obtained, which indicates a negative correlation. Next, we evaluated the subgroups of patients stratified by blood caffeine concentrations (<20 mg/L [non-toxic] or ≥20 mg/L [toxic]),[5] and a ROC curve was created using potassium values, and the cut-off value for the toxic region was calculated. Figure 2 shows the ROC curve of blood caffeine concentration of 20 mg/L or higher and the serum potassium level. The AUC was 0.716 and sensitivity and specificity were 0.829 and 0.568, respectively; the cut-off value for the serum potassium level was 3.3 mEq/L at a blood caffeine concentration of 20 mg/L. Figure 3 shows a ROC curve of blood caffeine concentrations of 80 mg/L or higher and the serum potassium level. The AUC was 0.888, with sensitivity and specificity of 0.919 and 0.818 respectively, for a serum potassium cut-off value of 2.9 mEq/L (lethal dose) at blood caffeine concentrations of 80 mg/L.

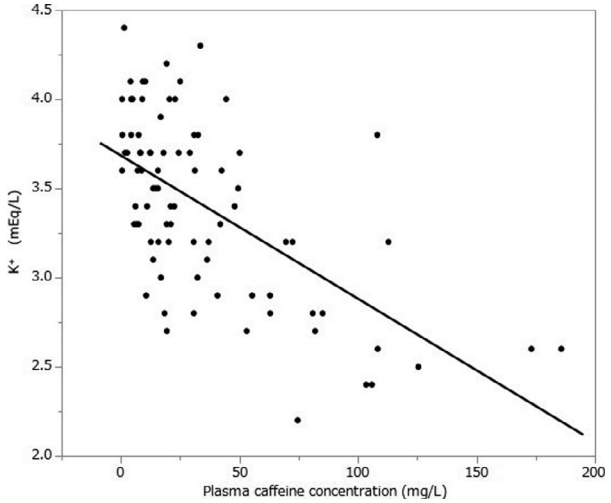

Fig. 1. Scatterplot of serum potassium levels and blood caffeine concentrations in 85 patients treated for acute caffeine poisoning.

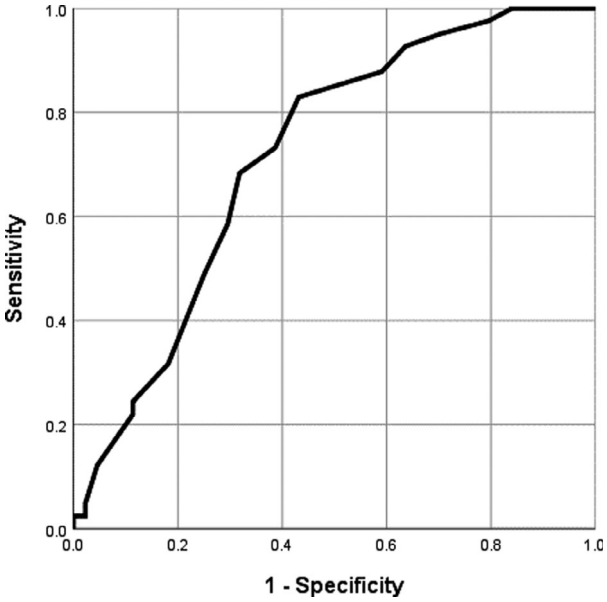

Fig. 2. Receiver operating characteristic (ROC) curve of blood caffeine concentrations higher than 20 mg/L and serum potassium levels in 85 patients treated for acute caffeine poisoning. Area under the ROC curve, 0.716 (95% confidence interval, 0.606–0.825); sensitivity, 0829; specificity, 0.568; and cut-off point, 3.3.

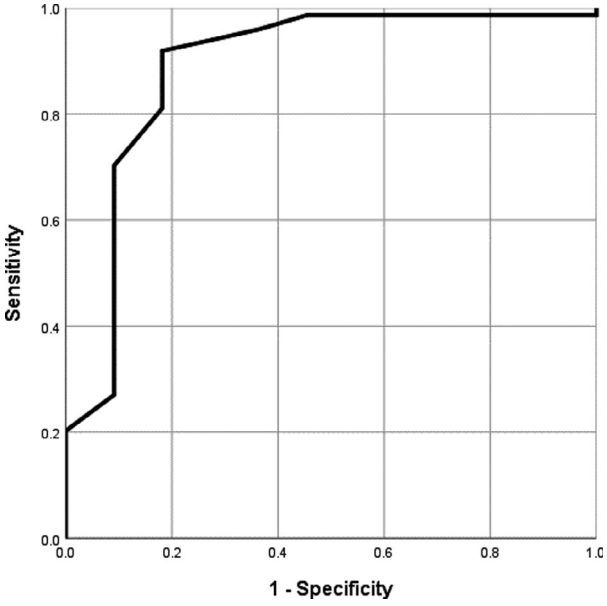

Fig. 3. Receiver operating characteristic (ROC) curve of blood caffeine concentrations higher than 80 mg/L and serum potassium levels in 85 patients treated for acute caffeine poisoning. Area under the ROC curve, 0.888 (95% confidence interval, 0.756–1.000); sensitivity, 0.919; specificity, 0.818; cut-off point, 2.9.

DISCUSSION

CAFFEINE ACTS ANTAGONISTICALLY at the adenosine receptor and increases the levels of cyclic adenosine monophosphate (cAMP) by inhibiting phosphodiesterase.[7,8] The mechanism of caffeine-induced hypokalemia is theorized to be as follows. Caffeine competitively binds to adenosine receptors A1 and $A2_A$, stimulates neuroexcitation, activates Na-K ATPase through the β2 receptor, and shifts K^+ from the plasma into intracellular fluid. Blockage of adenosine receptors inhibits K^+ efflux across adenosine triphosphate-dependent potassium channels across cell membranes. Caffeine's inhibition of phosphodiesterase, increasing intracellular cAMP, maintains Na-K ATPase activity, and thereby promotes intracellular translocation of K^+. In addition, the adenosine β2 receptor is stimulated and neutral lipolysis is carried out by antagonism of the adenosine β1 receptor. Glycerol produces glucose by gluconeogenesis, causing blood glucose levels to increase, and blood glucose enters cells together with insulin. K^+ efflux decreases serum levels of potassium, and caffeine could cause excessive excretion of K^+ due to its diuretic effect. In addition, hypokalemia due to respiratory alkalosis secondary to the increased respiratory rate has previously reported.[9]

Several studies have reported a relationship of hypokalemia with caffeine intoxication.[10,11] In addition, hypokalemia has been reported in consumption of caffeine-containing energy drinks and beverages such as cola. According to Kamijo *et al*., 82 (84.5%) of 97 patients with caffeine addiction had hypokalemia.[12] It is clear that acute caffeine poisoning results in low potassium, although there is no report of the relationship between caffeine concentration and hypokalemia. In this study, we found a negative correlation of −0.612 for this association, indicating a correlation between serum potassium and the blood caffeine concentration. In addition, we found that if the serum potassium was 3.3 mEq/L or less, the possibility of poisoning was in the toxic range, and levels of 2.9 mEq/L or lower indicated a high possibility of lethality. In patients suspected of acute caffeine poisoning, serum levels of potassium can guide diagnosis when blood levels of caffeine cannot be measured immediately. Likewise, it is important to consider caffeine poisoning in cases where hypokalemia is detected in patients with unexplained acute toxicity.

Hypokalemia has been associated with prolonged QT on electrocardiograms, ventricular arrhythmias, and sudden death.[13–15] Therefore, it is necessary to correct serum levels of potassium and periodically evaluate the electrocardiogram and serum potassium levels in patients with toxicity. In addition, the report indicated that propranolol could be given for hypokalemia caused by elevation of catecholamine and β2 agonists.[16] Caffeine has a plasma protein binding of 36%, and hemodialysis has been reported to be effective to reduce blood caffeine concentration.[17,18]

Limitations

We included only 85 cases, and this small sample size is a limitation of this research. Therefore, it is necessary to increase the number of cases to detect more accurate results.

CONCLUSION

SERUM POTASSIUM LEVELS correlate with blood caffeine levels in patients who consume large quantities of caffeine. Serum potassium levels were estimated from caffeine blood concentrations in the toxic range to be 3.3 mEq/L or lower, and serum potassium levels were estimated from lethal caffeine blood levels to be 2.9 mEq/L or lower. Serum potassium levels can be a parameter that correlates with blood caffeine levels.

DISCLOSURE

Approval of the research protocol: This study was carried out with the approval of the institutional ethics committee of the hospital (20R-103).
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

REFERENCES

1 U.S. Department of Health and Human Services Food and Drug Administration Center [homepage on the internet]. Pure and Highly Concentrated Caffeine [updated September 2018; cited 1 February 2020]. Available from: https://www.fda.gov/food/dietary-supplement-products-ingredients/pure-and-highly-concentrated-caffeine.
2 Departments and Agencies of Public Service and Military, Canada [homepage on the internet]. Health Canada is advising Canadians about safe levels of caffeine consumption (2017) [updated May 2017; cited 1 February 2020]. Available from: https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/63362a-eng.php.
3 European Food Safety Authority [homepage on the internet]. Caffeine [updated 2015; cited 1 February 2020]. Available from http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/efsaexplainscaffeine150527.pdf.

4 Willson C. The clinical toxicology of caffeine: A review and case study. Toxicol. Rep. 2018; 5: 1140–52.
5 Uges DRA. Blood level data. In: Brandenberger H, Maes RAA (eds). Analytical Toxicology for Clinical, Forensic and Pharmaceutical Chemists. Berlinde Gruyter, 1997; 707–14.
6 Higdon JV, Frei B. Coffee and health: A review of recent human research. Crit. Rev. Food Sci. Nutr. 2006; 46: 101–23.
7 Bradberry SM, Vale JA. Disturbances of potassium homeostasis in poisoning. J. Toxicol. Clin. Toxicol. 1995; 33: 295–310.
8 Gernnari FJ. Hypokalemia. N. Engl. J. Med. 1998; 339: 451–8.
9 Rieg T, Steigeke H, Schnermann J, Richter K, Osswald H, Vallon V. Requirement of intact adenosine A1 receptors for the diuretic and natriuretic action of the methylxanthines theophylline and caffeine. J. Pharmacol. Exp. Ther. 2005; 313: 403–9.
10 Tajima Y. Coffee-induced hypokalemia. Clin. M. Insights. 2010; 3: 9–13.
11 Tsimihodimos V, Kakaidi V, Elisaf M. Cola-induced hypokalemia: pathophysiological mechanisms and clinical implication. J. Clin. Pract. 2009; 63: 900–2.
12 Kamijo Y, Takai M, Fujita Y, Usui K. A retrospective study on the epidemiological and clinical features of emergency patients with large or massive consumption of caffeinated supplements or energy drink in Japan. Intern. Med. 2018; 57: 2141–6.
13 Rottaleaender D, Motloch LJ, Reda S, Larbig R, Hoppe UC. Cardiac arrest due to long QTs syndrome associated with excessive consumption of energy drink. Int. J. Cardiol. 2012; 158: e51–e52.
14 Zuchinali P, Ribeiro PA, Pimentel M, da Rosa PR, Zimerman LI, Rohde LE. Effect of caffeine on ventricular arrhythmia: a systematic review and meta-analysis of experimental and clinical studio. Europace 2016; 18: 257–66.
15 Kozik TM, Shah S, Bhattacharyya M, *et al*. Cardiovascular response to energy drink in a healthy population: The c-energy study. Am. J. Emerg. Med. 2016; 34: 1205–9.
16 Struthers AD, Elliott HL, Reid JL. Metabolic consequences of salbutamol poisoning reversed by propranolol. Br. Med. J. (Clin. Res. Ed.). 1982; 285: 1655–6.
17 Fausch K, Uehlinger DE, Jakob S, Pasch A. Haemodialysis in massive caffeine intoxication. Clin. Kidney J. 2012; 5: 150–2.
18 Clausen T. Hormonal and pharmacological modification of plasma potassium homeostasis. Fundam. Clin. Pharmacol. 2010; 24: 595–605.