Original Article

Urinary glucose and ketone bodies as indicators of acute caffeine poisoning

Seiji Morita, Tomoatsu Tsuji, Mari Amino, Naoya Miura, Takeshi Saito, and Yoshihide Nakagawa

Department of Emergency and Critical Care Medicine, Tokai University School of Medicine, Isehara, Japan

Aim: In various countries, many fatal health problems have been reported due to high intake of caffeine-rich energy drinks, tablets, and powders. In patients with acute caffeine poisoning, determination of blood caffeine concentration is an important yet difficult task. We aimed to assess whether the presence of glucose and ketone bodies in urine reflected the blood caffeine concentration in patients with acute caffeine poisoning.

Methods: From April 2010 to March 2018, 25 patients with an overdose of only caffeine-rich tablets were admitted to our hospital. Their clinical features were investigated. In addition, we investigated whether the glucose and ketone bodies in the urine reflected blood caffeine concentration in 23 patients who underwent the urine qualitative test at admission.

Results: The majority of the patients were young healthy women, whose average caffeine ingestion was 15.6 ± 8.1 g. Initial urine examinations showed glucose in 60% (14/23) of patients and ketone bodies in 57% (13/23) of patients. Ketone bodies or glucose were found in 78% (18/23) of the patients. The correlation between blood caffeine concentration and urinary glucose was $R = 0.625$, blood caffeine concentration and ketone bodies was $R = 0.596$, and blood caffeine and both was $R = 0.76$.

Conclusion: Urine qualitative test is effective for differential diagnosis and severity assessment of acute caffeine poisoning in patients.

Key words: Acute caffeine poisoning, blood caffeine concentration, caffeine, overdose, urine qualitative test

INTRODUCTION

CAFFEINE, A NATURALLY derived compound found in coffee beans, tea leaves, and cacao beans, is classified as a relatively safe compound.[1] Recently, many caffeine-rich energy drinks and over-the-counter supplements have been sold as appetite suppressants, revitalizers, and high-performance supplements.[2,3] However, many fatal health problems have been reported due to the combined use of alcohol and energy drinks, and their overdose.[3–5] Several case reports and forensic reports on acute caffeine poisoning have already been published.[6–10]

In patients with acute caffeine poisoning, blood caffeine concentration plays a major role in treatment strategy, which is difficult to measure in real time. In 2014, we reported the correlation between blood lactate concentration and blood caffeine concentration in acute caffeine poisoning.[11] This study aimed to assess whether the urine qualitative test (urinary glucose and ketone bodies) is simpler and more effective than the measurement of blood lactate concentration in reflecting blood caffeine concentration in patients with acute caffeine poisoning.

Corresponding: Seiji Morita, MD, PhD, Department of Emergency and Critical Care Medicine, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan. E-mail: ermorita@msn.com.

Received 11 Nov, 2019; accepted 3 Feb, 2020

Funding Information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

METHODS

FROM APRIL 2010 to March 2018, 25 patients with acute caffeine poisoning due to only caffeine-rich tablets were admitted to our Trauma and Emergency Center. Their clinical parameters were recorded for this study.

Among them, the results of 23 patients who underwent a urine qualitative test using the urine dipstick during admission were assessed for the levels of glucose and ketone bodies in the urine to determine whether the levels reflected blood caffeine concentration.

Glucose is easily filtered in the glomerulus but is not present in the urine because the filtered glucose is normally reabsorbed. Therefore, a negative value is normal and ranges from 1+ to 4+, depending on the glucose concentration. When the

Table 1. Clinical features of 25 patients with acute caffeine poisoning

No.	Gender	Age	BMI	Estimated intake		Medical history		GCS	HR	RR	sBP	BCC	BG	Urine		Sum	Outcome
		(years)		Total (g)	mg/kg	Physical	Psychiatric		(b.p.m.)	(/min)	(mmHg)	(μg/mL)	(mg/dL)	Glucose	Ketone		
1	F	19	19.8	14	311	–	–	15	108	36	112	42.8	130	1	0	1	Survived
2	M	24	18.8	10	139	–	–	15	122	32	120	56.3	134	0	2	2	Survived
3	F	46	21.8	8	127	–	–	14	135	18	122	52.7	148	2	1	3	Survived
4	M	39	18.9	12	171	–	–	15	77	20	124	17.8	98	0	0	0	Survived
5	F	16	21.0	12	214	–	+	15	100	20	106	20.7	106	0	0	0	Survived
6	F	23	28.4	21	350	–	–	13	164	24	136	205.1	221	3	2	5	Survived
7	F	24	28.4	22	407	–	–	15	124	26	102	53.0	119	0	0	0	Survived
8	F	31	20.7	24	414	–	–	15	122	31	142	62.9	150	1	1	2	Survived
9	F	17	23.6	12	162	–	–	15	109	22	100	31.4	135	0	0	0	Survived
10	M	38	20.7	24	429	–	–	13	148	16	106	173.2	168	3	1	4	Survived
11	M	24	19.8	10	132	–	+	15	126	33	112	58.0	119	–	–	–	Survived
12	F	20	29.9	8	167	–	–	14	130	28	136	82.0	142	2	0	2	Survived
13	M	44	19.2	12	203	–	–	15	112	20	128	42.0	136	0	1	1	Survived
14	F	28	18.7	9	164	–	–	15	118	19	132	56.0	140	0	1	1	Survived
15	F	21	16.5	21	339	–	–	14	110	22	122	77.0	144	1	0	1	Survived
16	F	23	27.7	19	365	–	–	15	102	26	108	45.0	182	2	1	3	Survived
17	F	28	25.5	22	407	–	+	15	144	29	98	65.0	140	1	1	2	Survived
18	M	18	18.7	22	282	–	–	15	122	20	132	40.0	108	1	0	1	Survived
19	M	21	24.1	37.5	60	–	–	15	98	24	130	105.9	162	4	0	4	Survived
20	F	19	18.7	10	169	–	–	15	98	18	118	81.9	178	3	3	6	Survived
21	F	28	18.6	7.2	103	–	+	15	124	23	100	125.5	156	0	2	2	Survived
22	F	22	22.3	4.8	96	–	+	13	104	18	128	108.3	138	1	1	2	Survived
23	M	30	27.1	15	221	–	+	14	180	20	120	173.2	140	–	–	–	Survived
24	F	23	20.4	6.3	126	–	+	15	110	26	108	11.1	124	0	0	0	Survived
25	F	16	28.4	28.4	394	–	–	14	76	18	130	185.8	188	3	3	6	Survived

BCC, blood caffeine concentration; BG, blood glucose; BMI, body mass index; F, female; GCS, Glasgow Coma Scale; HR, heart rate; M, male; RR, respiratory rate; sBP, systolic blood pressure.

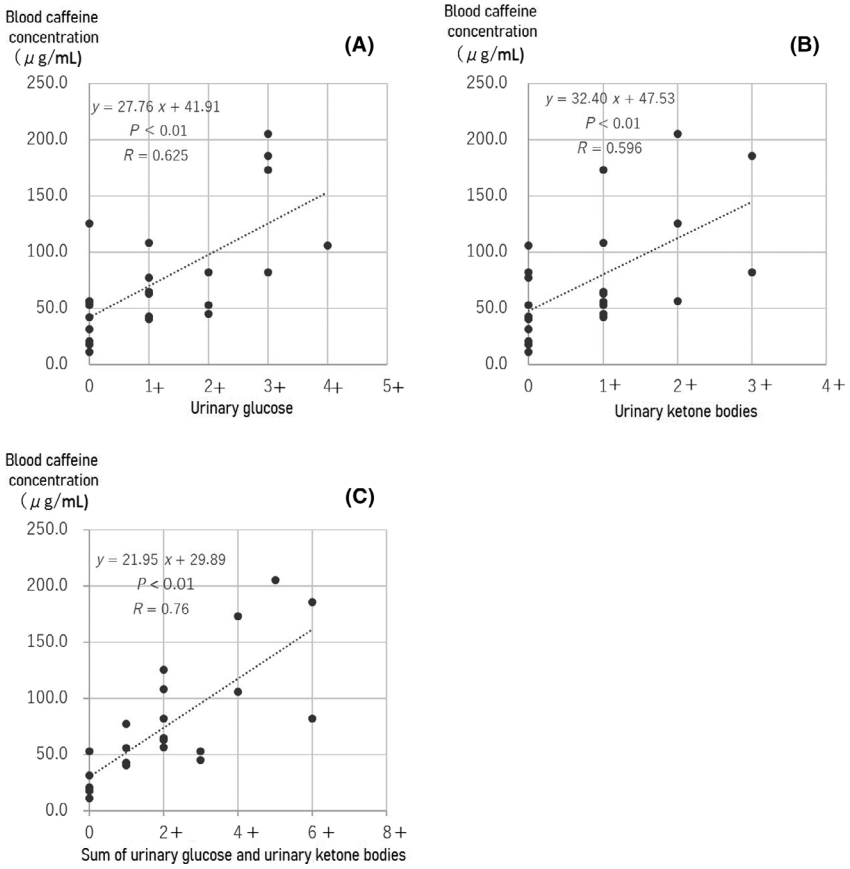

Fig. 1. Correlation graphs of (A) urinary glucose and blood caffeine concentration, (B) urinary ketone bodies and blood caffeine concentration, (C) both urinary glucose and ketone bodies and blood caffeine concentration in patients with acute caffeine poisoning patients.

intermediate products of fatty acid metabolism exceed the ability of the body to metabolize these compounds, ketone bodies accumulate in the blood and urine. However, urinary ketone bodies do not react qualitatively. Therefore, a negative value is normal and ranges from 1+ to 3+, depending on the amount of ketone bodies in the urine.

The correlation was analyzed by plotting blood caffeine concentration on the vertical axis; the urinary glucose (negative, 1+, 2+, 3+, and 4+), urinary ketone bodies (negative, 1+, 2+, and 3+), and sum of the two (negative, 1+, 2+, 3+, 4+, 5+, 6+, and 7+) on the horizontal axis. The urinalysis in this study used Uro-PaperIII (Eiken Chemical Co., Tokyo, Japan). Statistical analysis software (IBM SPSS Statistics version 26) was used for data analysis (Spearman's rank correlation coefficient). Data are presented as mean ± standard deviation.

RESULTS

CLINICAL PARAMETERS OF the 25 patients are shown in Table 1. The average age was 25.7 ± 8.3 years, and the majority of patients were young healthy women with an average caffeine ingestion of 15.6 ± 8.1 g. Initial vital signs showed that consciousness was either normal or mildly disturbed with tachycardia or tachypnea. No extreme hypotension or hypertension was observed. In the initial blood examination, the average blood caffeine concentration and average blood glucose level were 78.9 ± 54.6 μg/mL and 144.2 ± 27.8 mg/dL, respectively. In their initial urine examination, 60% (14/23) of patients had glucose and 57% (13/23) of patients had ketone bodies. Ketone bodies or glucose in the urine were found in 78% (18/23) of patients.

The correlation coefficients between blood caffeine concentration and glucose in the urine was 0.625 (Fig. 1A), between blood caffeine concentration and ketone bodies in the urine was 0.596 (Fig. 1B), and blood caffeine concentration and sum of the two in urine was 0.760, which were comparatively higher (Fig. 1C).

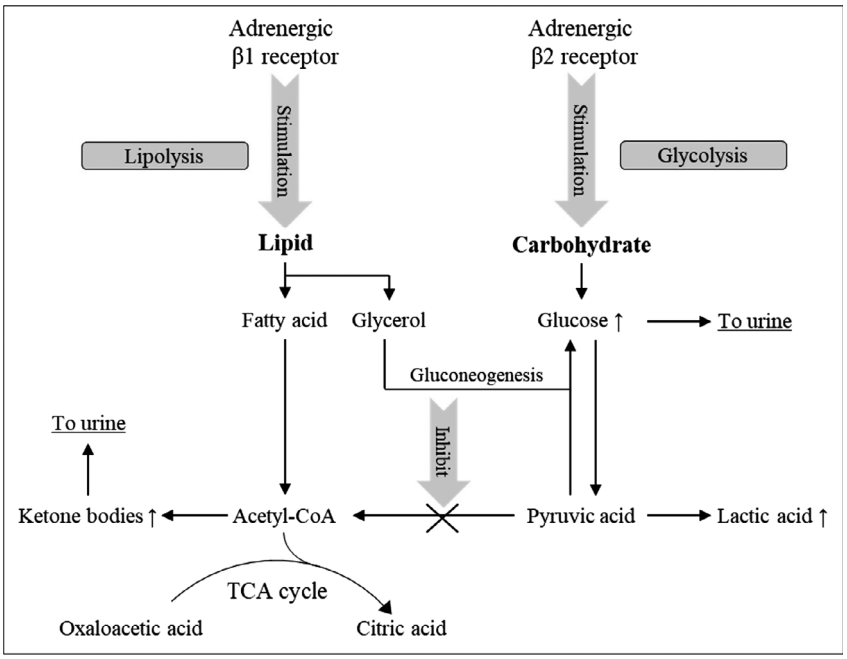

Fig. 2. Mechanisms of production of urinary glucose and ketone bodies in acute caffeine poisoning. TCA, tricarboxylic acid.

DISCUSSION

CAFFEINE, A CENTRAL nervous system stimulant of the methylxanthine class, is the world's most widely consumed psychoactive drug as it is unregulated.[1,2] In normal doses, there are three main mechanisms: (i) release of calcium from intracellular stores, (ii) inhibition of phosphodiesterase, (iii) antagonism of central and peripheral adenosine receptors. Because presynaptic adenosine receptors are blocked, the systemic release of catecholamines is increased.[12–14] Due to this, caffeine awakens the central nervous system, reducing fatigue and sleepiness and improving reaction time, concentration, and motor control.

In contrast, high doses of caffeine can lead to many fatal health problems, which have been reported in various countries.[2,6–9,12,15] Therefore, many organizations and countries are calling attention to the overconsumption of caffeine preparations.[16–18] However, there are still many countries, including Japan, where they can be easily purchased over the counter. The symptoms of acute caffeine poisoning include electrolyte imbalance (hypokalemia and hyponatremia), lethal dysrhythmia, hypotension, convulsion, respiratory failure, lactic acidosis, and rhabdomyolysis.[8,19–21] The severity of acute caffeine poisoning depends on the blood caffeine concentration, which requires specialized techniques for its measurement. In Japan, Kamijo *et al.* undertook retrospective and multicenter studies on 101 patients who consumed high quantities of caffeinated supplements or energy drinks.[21] However, only 17% (17/101) of patients had caffeine blood concentrations measured during admission, and whether it was measured in real time remained unclear. Therefore, a simple indicator of blood caffeine concentration is important.

Schmidt and Karlson-Stiber concluded that caffeine results in excessive sympathetic stimulation, which leads to lactic acidosis[15] (Fig. 2). This served as a basis for our study in 2014, in which we reported the correlation between blood lactate levels and blood caffeine concentrations in patients with acute caffeine poisoning.[14] We later realized that the mechanisms of production of urinary glucose and ketone bodies were similar to those of lactic acidosis and concluded that a urine qualitative test was a much simpler alternative. Although lactate is a highly correlated factor of caffeine blood concentration, it is dependent on many factors including convulsions and shock. Therefore, using both as indicators is effective in many situations.

The mechanisms of production of urinary glucose and ketone bodies are shown in Figure 2. In acute caffeine poisoning, excessive beta-1 adrenergic receptor stimulation promotes lipolysis, producing increased levels of fatty acids and glycerol. These fatty acids are converted to acetyl-CoA by beta-oxidation, which is used in the tricarboxylic acid cycle. Any unused acetyl-CoA is converted into ketone bodies, which enters the blood stream and consequently urine.

In another pathway, excessive stimulation of beta-2 adrenergic receptor promotes glycolysis and raises blood glucose

levels, some of which enters the urine. Some glucose is converted to pyruvate. However, pyruvate dehydrogenase is inhibited to prevent pyruvate conversion to acetyl-CoA, and hence, gluconeogenesis occurs from glycerol. These mechanisms result in hyperglycemia, resulting in the appearance of urinary glucose. In our patients, the average blood glucose level was high (144.2 mg/dL) and urinary ketone bodies or glucose was found in 78% (18/23) of them. The balance between glucose and ketone bodies in urine is unclear, but the sum of both correlated with blood caffeine concentration.

LIMITATION

IN THIS STUDY, patients with diabetes or other illnesses were not included and hence, it might not be effective in such cases.

CONCLUSION

BASED ON OUR findings, the urine qualitative test is a very simple and effective method that can be carried out at the clinic to assess the initial severity of acute caffeine poisoning in patients.

DISCLOSURE

Approval of the research protocol: This study was conducted with the approval of the institutional ethics committee of the hospital (18R-112).
Informed consent: None.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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