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【 ORIGINAL ARTICLE 】

A Retrospective Study on the Epidemiological and Clinical Features of Emergency Patients with Large or Massive Consumption of Caffeinated Supplements or Energy Drinks in Japan

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Abstract:

Objective We conducted a retrospective study on the epidemiological and clinical features of patients with acute caffeine poisoning in Japan.

Methods Letters requesting participation were sent to 264 emergency departments of hospitals, and questionnaires were mailed to those that agreed to participate.

Patients Participants were patients transported to emergency departments of hospitals between April 2011 and March 2016 after consuming large or massive amounts of caffeinated supplements and/or energy drinks (caffeine dose ≥1.0 g).

Results We surveyed 101 patients from 38 emergency departments. Since April 2013, the number of patients has markedly increased. Of these young patients (median age, 25 years), 53 were men, and 97 had consumed caffeine in tablet form. Estimated caffeine doses (n=93) ranged from 1.2 to 82.6 g (median, 7.2 g). Serum caffeine levels on admission (n=17) ranged from 2.0 to 530.0 μg/mL (median level, 106.0 μg/mL). Common abnormal vital signs and laboratory data on admission included tachypnea, tachycardia, depressed consciousness, hypercreatinekinasemia, hyperglycemia, hypokalemia, hypophosphatemia, and hyperlactatemia. Common signs and symptoms in the clinical course included nausea, vomiting, excitement/agitation, and sinus tachycardia. Seven patients (6.9%) who had consumed ≥6.0 g of caffeine, or whose serum caffeine levels on admission were ≥200 μg/mL, developed cardiac arrest. Ninety-seven patients (96.0%) recovered completely, but 3 patients (3.0%) died.

Conclusion The present analysis of data from more than 100 emergency patients revealed clinical features of moderate to fatal caffeine poisoning. We recommend highlighting the toxicity risks associated with ingesting highly caffeinated tablets.

Key words: caffeine, caffeinated supplements, caffeinated energy drinks, poisoning

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Introduction

Caffeine (1,3,7-trimethylxanthine), a natural alkaloid derived from tea leaves, coffee beans, cocoa beans, and kola nuts, has long been recognized as an addictive, mild stimulant (1). Aside from in tea, coffee, chocolate, and most soft drinks, caffeine is also present in various prescription drug mixtures and over-the-counter (OTC) drugs, such as cold medicines, at doses of 30 to 200 mg (2). In addition, supplements with drowsiness- and fatigue-combating effects or energy drinks with stimulatory and performance-enhancing effects contain caffeine at doses of 50 to 505 mg (2, 3).

In Japan, several severe or fatal cases have been reported

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among people who consumed large or massive amounts of caffeinated supplements (4, 5). On December 21, 2015, the Department of Forensic Medicine (Faculty of Medicine, Fukuoka University) announced that a forensic autopsy detected an extraordinarily high concentration of caffeine in the blood of a man in his 20s who had died after frequently ingesting caffeinated energy drinks, according to witnesses. The mass media pounced on this incident as the first fatality among people who regularly consume excess quantities of caffeinated energy drinks in Japan, although a large number of caffeinated tablets were also found in his stomach postmortem.

The Japanese Society of Clinical Toxicology (JSCT), an academic society of clinical toxicologists (consisting of physicians, pharmacists, and other researchers affiliated with hospitals, universities, and institutions), conducted a retrospective study on the epidemiological and clinical features of emergency patients with acute poisoning following the ingestion of large or massive quantities of caffeinated supplements or energy drinks in Japan.

Materials and Methods

At the beginning of April 2016, we sent letters requesting participation and asking for faxed replies within 2 weeks to 264 emergency departments with employees (physicians, pharmacists, and researchers) who were members of the JSCT. Participants were patients transported to the emergency departments of hospitals between April 2011 and March 2016 after consuming large or massive amounts of supplements and/or energy drinks containing caffeine as a main ingredient (caffeine dose ≥1.0 g), as well as other much less pharmacologically active ingredients, such as vitamins, sugars, and amino acids. Patients who reported having consumed these caffeinated products, who were witnessed using such products, or who were found to be in possession of residual products at the scene were included in the study. Patients who consumed large or massive amounts of prescription drug mixtures or OTC drugs containing pharmacologically active ingredients, such as acetaminophen or ibuprofen as well as caffeine, and patients who simultaneously overdosed using other drugs were excluded from the study.

At the beginning of May 2016, participating emergency departments were mailed a questionnaire that included close-ended questions regarding the following: patient age and gender, commercial names and consumed amounts of the caffeinated products, caffeine dose, vital signs and laboratory data on arrival at the emergency departments, clinical signs and symptoms, physical complications during the clinical course, treatments [including ventilator, hemodialysis (HD), direct hemoperfusion (DHP), and percutaneous cardiopulmonary support (PCPS)], outcomes, and results of toxicological analyses of blood. The pilot questionnaire was tested for simplicity in understanding and time required for completion. Physicians, pharmacists, and researchers of the participating emergency departments were asked to search for all patients satisfying the above conditions using information available in patient medical records/databases and to complete the questionnaire for every case they found. A reminder which might have increased the response rate was not sent out. All questionnaires completed by the end of June 2016 were collected and analyzed at the Emergency Medical Center and Poison Center of Saitama Medical University Hospital. This study was approved by the ethics committees of all participating hospitals.

Hypercreatinekinasemia was defined as serum creatine kinase (CK) ≥200 IU/L; hyperglycemia as serum glucose ≥180 mg/dL; hypokalemia as serum K^+ ≤3.4 mmol/L; hypophosphatemia as serum inorganic phosphate (IP) ≤2.4 mg/dL; and hyperlactatemia as serum lactate ≥2.0 mmol/L. Tachypnea was defined as a respiratory rate (RR) ≥20 breaths/minute; depressed consciousness as a Glasgow Coma Scale (GCS) score of 3 to 14; tachycardia as heart rate (HR) ≥100 beats/minute; and hyperthermia as body temperature (BT) ≥37.5℃. Acute kidney injury was defined as ≥0.3 mg/dL or a 1.5-fold increase from arrival in serum creatinine (Cr). Liver injury was defined as alanine aminotransferase (ALT) ≥80 IU/L (twice the upper limit of the normal). Acute respiratory distress syndrome (ARDS) was defined as follows: acute onset, bilateral pulmonary infiltrates consistent with the presence of edema, and impaired oxygenation with a PaO_2/FIO_2 ratio ≤200, excluding clinical evidence of left atrial hypertension. Rhabdomyolysis was defined as CK ≥10,000 IU/L (50 times the upper limit of normal) with myoglobinuria.

Statistical analyses

Spearman's rank correlation coefficients between clinical variables and serum caffeine levels or estimated caffeine doses and between serum caffeine levels and estimated caffeine doses were calculated.

Results

Study population

A total of 160 patients from 38 (14.4%) emergency departments of hospitals in Japan were evaluated. Forty-nine patients who consumed large or massive amounts of prescription drug mixtures or OTC drugs containing pharmacologically active ingredients as well as caffeine, 8 patients who simultaneously overdosed using other drugs such as benzodiazepines, and 2 patients who were transported by ambulance after April 2016 were excluded. Thus, a total of 101 patients were included in this study. The annual number of patients has increased markedly, from 10 (April 2011 to March 2012) and 5 (April 2012 to March 2013) to 24 (April 2013 to March 2014), and has continued to increase gradually since then, to 25 (April 2014 to March 2015) and 37 (April 2015 to March 2016).

Table 1. Vital Signs and Laboratory Data on Admission.

Vital signs[a]	No.	%
RR (breaths/minute)		
≤19	41	42.7
20-29	39	40.6
30-39	16	16.7
Total	96	100.0
SBP (mmHg)		
≤89	5	5.1
90-139	75	76.5
140-179	18	18.4
Total	98	100.0
HR (beats/minute)		
≤59	1	1.0
60-99	39	39.8
100-139	47	48.0
140≤	11	11.2
Total	98	100.0
GCS		
3-8	4	4.1
9-14	32	32.7
15	62	63.3
Total	98	100.0
BT (°C)		
≤34.9	6	6.4
35.0-37.4	83	88.3
37.5-38.4	4	4.3
38.5≤	1	1.1
Total	94	100.0

Blood chemistry	No.	%
ALT (IU/L) (NR: 5-39)		
≤39	74	76.3
40-79	15	15.5
80-199	5	5.2
200≤	3	3.1
Total	97	100.0
Cr (mg/dL) (NR: 0.40-0.99)		
≤0.99	83	86.4
1.00-1.29	11	11.5
1.30≤	2	2.1
Total	96	100.0
CK (IU/L) (NR: 20-199)		
≤199	55	58.5
200-1,999	32	34.0
2,000-9,999	6	6.4
10,000≤	1	1.1
Total	94	100.0
Glucose (mg/dL) (NR: 70-109)		
70-109	7	7.7
110-179	41	45.1
180≤	43	47.3
Total	91	100.0
K^+(mmol/L) (NR: 3.5-4.9)		
≤2.4	17	17.5
2.5-3.4	65	67.0
3.5-4.9	12	12.4
5.0≤	3	3.1
Total	97	100.0
IP (mg/dL) (NR: 2.5-4.9)		
≤1.4	10	21.7
1.5-2.4	17	37.0
2.5-4.9	15	32.6
5.0≤	4	8.7
Total	46	100.0
Lactate (mmol/L) (NR: 0.5-1.9)		
≤1.9	49	66.2
2.0-3.9	8	10.8
4.0≤	17	23.0
Total	74	100.0

[a]Vital signs of two cardiopulmonary-arrested patients on admission were excluded. RR: respiratory rate, SBP: systolic blood pressure, HR: heart rate, GCS: Glasgow Coma Scale, BT: body temperature, ALT: alanine aminotransferase, Cr: creatinine, CK: creatine kinase, IP: inorganic phosphate, NR: normal range

Table 2. Spearman's Rank Correlation Coefficients between Clinical Variables and Estimated Caffeine Doses or Serum Caffeine Levels.

	Estimated caffeine dose (n=93)	
	Correlation coefficient	p value
RR	0.23	0.03
GCS	-0.22	0.04
ALT	0.25	0.02
Glucose	0.30	0.00
K^+	-0.41	0.00
	Serum caffeine level (n=17)	
	Correlation coefficient	p value
SBP	-0.75	0.00
GCS	-0.61	0.02
Glucose	0.59	0.02

RR: respiratory rate, GCS: Glasgow Coma Scale, ALT: alanine aminotransferase, SBP: systolic blood pressure

Patient demographics

Most patients were young (median age, 25 years; range, 14 to 54 years). Slightly more men (53 patients, 52.5%) than women experienced an acute reaction. Ninety-seven patients (96.0%) reported having consumed caffeine in tablet form and 10 (9.9%) in liquid form. Five patients (5.0%) reported that they had consumed coffee simultaneously with these products. With respect to tablets, 75 patients (74.3%) reported having consumed Estaron-mocha® products (SS Pharmaceutical, Tokyo, Japan). Estaron-mocha tablets® contain 100 mg of caffeine and vitamin B_1 per tablet, and Estaron-mocha 12® contain 100 mg of caffeine as well as vitamin B_1, B_6, and B_{12} per tablet. For liquids, 6 patients (5.9%) reported having consumed Monster Energy® (Asahi Soft Drinks, Tokyo, Japan) containing 142 mg of caffeine per 355-mL can, and 2 patients (2.0%) reported having consumed Red Bull® (Red Bull Japan, Tokyo, Japan) containing 80 mg of caffeine per 250-mL can. Based on information from commercial names and consumed amounts of caffeinated products referred by ambulance staffs, caffeine doses of 93 patients (92.1%) were able to be estimated (median, 7.2 g; range, 1.2 to 82.6 g). The remaining 8 patients were presumed to have consumed at least ≥1.0 g of caffeine. The serum caffeine levels on admission were measured only in 17 patients (16.8%) (median, 106.0 μg/mL; range, 2.0 to 530.0 μg/mL). The time intervals between caffeine consumption and arrival at hospital were able to be estimated in 93 patients (median, 3.5 hours; range, 0.8 to 24.0 hours).

Clinical manifestations

Abnormal vital signs and laboratory data considered common on admission in ≥25% of patients included tachypnea (55/96, 57.3%), tachycardia (58/98, 59.2%), depressed consciousness (36/98, 36.7%), hypercreatinekinasemia (39/94, 41.5%), hyperglycemia (43/91, 47.3%), hypokalemia (82/97, 84.5%), hypophosphatemia (27/46, 58.7%), and hyperlactatemia (25/74, 33.8%). The vital signs of 2 cardiopulmonary-arrested patients on admission were excluded (Table 1). The estimated caffeine doses were positively correlated with the RR, ALT, and serum glucose level and negatively with the GCS score and serum K^+ level. The serum caffeine levels on admission were correlated positively with the serum glucose level and negatively with systolic blood pressure (SBP) and GCS score (Table 2). However, the serum caffeine levels were not significantly corre-

Table 3. Clinical Signs and Symptoms, and Organ Complications during Clinical Course (n=101).

Gastrointestinal symptoms	No.	%
Nausea	82	81.2
Vomiting	75	74.3
Abdominal pain	9	8.9
Hematemesis	4	4.0
Others	8	7.9
Neuropsychiatric symptoms	**No.**	**%**
Excitement, agitation	27	26.7
Headache	14	13.9
Irritability	10	9.9
Tremor	8	7.9
Delirium	4	4.0
Muscle spasms	3	3.0
Seizure	1	1.0
Myoclonus	1	1.0
Others	8	17.8
Cardiac symptoms	**No.**	**%**
Arrhythmia	60	59.4
Sinus tachycardia	51	50.5
VPC	10	9.9
Bigeminy	6	5.9
Supraventricular tachycardia	5	5.0
Ventricular tachycardia	2	2.0
Ventricular fibrillation	2	2.0
Others	2	2.0
Cardiac arrest	7	6.9
Hypotension (SBP ≤89 mmHg)	7	6.9
Others	5	5.0
Organ complications	**No.**	**%**
Liver injury	18	17.8
Acute kidney injury	6	5.9
ARDS	1	1.0
Rhabdomyolysis	1	1.0

VPC: ventricular premature conduction, ARDS: acute respiratory distress syndrome

lated with the estimated caffeine doses (Spearman's rank correlation coefficient: -0.201, p=0.454).

Signs and symptoms considered common during the clinical course of ≥25% of patients included nausea, vomiting, excitement/agitation, and sinus tachycardia. Notably, some patients developed cardiac arrest, but few exhibited seizures. Major organ complications included liver injury (Table 3).

Treatments and outcomes

Fourteen patients (13.9%) required ventilator support, 15 (14.9%) underwent hemopurification (HD: 11 patients, 10.9%; DHP: 4 patients, 4.0%), and 2 (2.0%) were treated with PCPS. Many patients were treated with medication as follows: metoclopramide (19 patients, 18.8%), benzodiazepines (e.g., midazolam, diazepam, and flunitrazepam) (10 patients, 9.9%), propofol (8 patients, 7.9%), potassium products (e.g., potassium chloride and potassium aspartate) (5 patients, 5.0%), fentanyl (5 patients, 5.0%), proton pump inhibitors (e.g., lansoprazole and omeprazole) (5 patients, 5.0%), β-blockers (e.g., landiolol and propranolol) (4 patients, 4.0%), antipsychotics (e.g., haloperidol and levomepromazine) (3 patients, 3.0%), and others.

Of the entire study population (n=101), 7 patients (6.9%) who had either consumed ≥6.0 g of caffeine or whose serum caffeine levels on admission were ≥200 μg/mL went into cardiac arrest and were intensively treated (Table 4). Eighty-five patients (84.2%) were admitted to the hospital, with a median length of hospitalization of 3 days (range, 1 to 42 days). Ninety-seven patients (96.0%) recovered completely, but 3 (3.0%) died, including 2 patients who exhibited cardiopulmonary arrest on admission. One patient was discharged with a moderate headache.

Discussion

Very few publications in the literature have focused on caffeine poisoning. The few publications that touch on the subject are case reports, most of which describe clinical courses or postmortem findings of fewer than 10 patients (2, 4-15). In the present study, a retrospective analysis of data from more than 100 patients who had consumed high doses of caffeine revealed clinical features of moderate to fatal caffeine poisoning. Although one study involved 43 patients, the caffeine doses described in that report (median, 1,040 mg; range, 600 to 1,500 mg) were much lower than those in the present study, with minor gastrointestinal symptoms being common, and none of the patients developing severe poisoning (16).

The present study showed an increase in the number of patients with caffeine poisoning since April 2013. Recently, the consumption of caffeinated supplements or energy drinks has been increasing in Japan, particularly among adolescents and young adults, due to the availability of such products through online purchases and in vending machines. Estaron-mocha tablet® and Estaron-mocha 12®, the most popular caffeinated supplements in Japan, have been marketed as OTC drugs since October 1973 and November 1998, respectively. With the revision of the Pharmaceutical Affairs Law in June 2009, Japanese websites, including the Rakuten Shopping Mall (Rakuten, Tokyo, Japan), began online sales of caffeinated supplements. Kirin Beverage (Tokyo, Japan) has owned the rights to sell Red Bull®, the most popular caffeinated energy drink in Japan, in vending machines since May 2013.

In the present study, most patients consumed caffeinated tablets, and a few consumed caffeinated liquids, although a few cases of severe poisoning after consuming a large number of caffeinated energy drinks have been previously reported overseas (17, 18). Energy drinks marketed in Japan contain 80 to 160 mg of caffeine per can; to reach the minimum lethal dose of caffeine in this study (6.0 g), a person would need to drink at least 37 cans of highly caffeinated energy drinks within a few hours. In comparison, consuming

Table 4. Patients who Developed Cardiac Arrest during Clinical Course.

Age/Gender (years)	Dose (g)	Level (μg/mL)	Treatment	Prognosis
20/M	20.0		Ventilator, HD, landiolol, propofol, fentanil	death
22/F	20.0	331	DHP	complete recovery
27/F	17.4	368	PCPS, ventilator, amiodarone KCl, magnesium sulfate	complete recovery
37/F	36.0		Ventilator, CHDF	complete recovery
27/F	6.0	232	Ventilator, HD	complete recovery
23/M (CPAOA)	6.0	530	PCPS, ventilator, landiolol, midazolam, propofol, epinephrine	death
22/F (CPAOA)	24.0		Epinephrine	death

Dose: estimated caffeine dose, Level: serum caffeine level on admission, M: male, F: female, CPAOA: cardiopulmonary arrest on arrival, PCPS: percutaneous cardiopulmonary support, HD: hemodialysis, DHP: direct hemoperfusion, CHDF: continuous hemodiafiltration

60 tablets containing 100 mg of caffeine would be much easier to achieve the same dose. In addition, a tablet containing 100 mg of caffeine can be obtained at a much cheaper price (less than a tenth) through online purchase than an energy drink containing the same dose of caffeine from a vending machine.

In the present study, seizures during the clinical course were rare, although a few pediatric cases of seizures have been reported (19). The youngest patient was 14 years old, and no young children (true pediatric patients) were included. Susceptibility to seizures may differ between adults and children. Hyperlactatemia on admission was common, although only a few cases of hyperlactatemia in severe-to-fatal instances of caffeine poisoning have been reported (20, 21). Blood lactate levels on admission were determined in only 73.3% of patients. Hyperlactatemia may tend to be overlooked in caffeine poisoning. Liver injury during the clinical course was observed often, although it has not been typically reported in cases of caffeine poisoning. Liver injury may be affected by medications or circulatory collapse to some extent in cases of severe-to-fatal caffeine poisoning. Various types of arrhythmia were also commonly noted. Arrhythmias, including bigeminy, supraventricular tachycardia, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation, as well as sinus tachycardia and cardiovascular collapse, have been previously reported (6-8).

In the present study, some patients were intensively treated. Theoretically, the mean plasma protein binding of caffeine (35%), its molecular size of 194 Da, and its volume of distribution (0.5 to 0.7 L/kg) make both DHP and HD effective methods of removing caffeine (4, 8, 22-26). PCPS may be indicated in patients who developed refractory ventricular arrhythmias (27).

Almost all patients in this study made a complete recovery. However, a few among those who developed cardiac arrest and consumed a large amount of caffeine or whose serum caffeine levels on admission were extremely high ultimately died. Fatalities among adults are relatively rare, with previous reports suggesting that fatalities likely result from ventricular arrhythmias, and death occurring at doses between 5 to 50 g and blood levels exceeding 80 to 100 μg/mL (2, 12-15).

Among those whose serum caffeine levels on admission were determined in the present study, the caffeine levels correlated with certain clinical variables, and four patients with extremely high levels went into cardiac arrest. Theophylline is another methylxantine that has a similar pharmacological profile to caffeine (28). In patients with theophylline poisoning, hemopurification (e.g., HD and DHP) is performed based on the severity of poisoning, as assessed by the blood levels of the substance (29). Similarly, it may be possible to evaluate the extent of caffeine poisoning and determine whether or not hemopurification should be performed based on the blood levels of caffeine.

In the present survey, most patients were transferred to the emergency department after the severity and blood caffeine levels had peaked, consistent with the fact that caffeine is easily absorbed from the intestinal tract and reaches maximum blood levels in about 2 hours. It may be important to educate the public to seek emergency help as soon as possible when a caffeine overdose is suspected.

Limitations

There are several limitations associated with this study. First, there may have been some selection bias due to the small number of emergency departments of hospitals involved in the study. Comparing clinical data among emergency departments can be problematic because the strategy of treatment, evaluation of organ injuries, and other factors can differ among emergency departments. Second, there was a lack of information regarding the intent of ingestion (i.e., whether ingestion was intentional, suicidal, or accidental), psychiatric treatment history, chronic use of caffeine preparations, toxicology screening performed to exclude any co-ingestion of other poisons, gastrointestinal decontamination, and serial changes in laboratory data, including serum potassium. Finally, not all patients were confirmed to have con-

sumed caffeinated products, as only a small number of biological samples were analyzed.

Conclusion

Caffeinated tablets may pose a higher risk of poisoning than caffeinated drinks, as tablets are much easier to consume in large or massive quantities. In 2004, Sweden restricted the maximum quantity of tablets containing 100 mg caffeine that can be bought over the counter in a single purchase (from 250 to 30). This restriction seemed to be effective in preventing suicides (30). We recommend highlighting the toxic risk of ingesting highly-caffeinated tablets and propose that caffeine be included as a substance to screen for in patients suspected of drug poisoning. A further prospective study with a toxicological analysis is warranted.

The authors state that they have no Conflict of Interest (COI).

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