Eur J Pediatr (2015) 174:1671–1678
DOI 10.1007/s00431-015-2581-x

SHORT COMMUNICATION

Prediction of plasma caffeine concentrations in young adolescents following ingestion of caffeinated energy drinks: a Monte Carlo simulation

Jung Woo Lee[1] **· Yookyung Kim**[1] **· Vidya Perera**[2,3] **· Andrew J. McLachlan**[3,4] **· Kyun-Seop Bae**[5]

Received: 21 January 2015 / Revised: 4 June 2015 / Accepted: 9 June 2015 / Published online: 26 June 2015

Abstract The fast-growing consumption of caffeinated energy drinks (CEDs) is linked to increasing reports of caffeine intoxication in adolescents. There is limited data available regarding plasma caffeine concentrations in this population after CED intake and the potential implications for caffeine-related toxicity. This study was an in silico population pharmacokinetic analysis of caffeine. Population pharmacokinetic model of oral caffeine was derived from a previous study of healthy male volunteers. Maximal plasma caffeine concentration (C_{max}) profiles following ingestion of one or two servings of popular CEDs were predicted using Monte Carlo simulation and available population body weight data of 10–15-year-old Korean adolescents. Caffeine C_{max} values were positively correlated with the amount of caffeine ingested in CEDs and negatively correlated with body weight. The median (range) C_{max} profiles varied from a low of 1.2 (0.5–2.6) mg/L to a concentration that is potentially associated with harmful caffeine-related effects of 25.4 (8.1–55.6) mg/L. A subgroup of female 10–11-year-old subjects exhibited the highest caffeine exposure profiles.

Conclusion: These data indicate that CED ingestion can increase the risk of serious caffeine intoxication in young adolescents, particularly those with low body mass.

What is Known:
- *Excessive consumption of caffeine can lead to serious caffeine intoxication.*
- *The risk of potential harmful caffeine intoxication after ingestion of caffeinated energy drinks (CED) has not been adequately evaluated in adolescents.*

What is New:
- *Predicted maximal plasma caffeine concentration profiles of adolescents with lower body weights showed an overlap with the ingested caffeine concentrations obtained from documented fatalities.*
- *The present simulation-based pharmacokinetic analysis demonstrates that CED ingestion could lead to potentially serious caffeine intoxication in this cohort.*

Communicated by Beat Steinmann

Revisions received: 29 May 2015 / 05 June 2015

✉ Kyun-Seop Bae
ksbae@amc.seoul.kr

Jung Woo Lee
jungwooku@gmail.com

Yookyung Kim
yookyung_kim@korea.ac.kr

Vidya Perera
vidyaper@buffalo.edu

Andrew J. McLachlan
Andrew.mclachlan@sydney.edu.au

1 Department of Human Ecology, College of Education, Korea University Graduate School, Seoul, Republic of Korea

2 School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, NY, USA

3 Faculty of Pharmacy, University of Sydney, Sydney, NSW, Australia

4 Center for Education and Research on Ageing, Concord Hospital, Concord, NSW, Australia

5 Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Keywords Adolescent · Caffeine · Energy drink · Monte Carlo method

Abbreviations

CED	Caffeinated energy drink
CL	Clearance
C_{max}	Maximal plasma caffeine concentration
k_a	Absorption rate constant
k_e	Elimination rate constant
MVN	Multivariate normal distribution
t_{max}	Time at which C_{max} is observed
V	Volume of distribution
η	Interindividual random variability parameter

Introduction

Caffeinated energy drinks (CEDs) typically contain high concentrations of caffeine and other additives and are rising in popularity. Strategic marketing of CEDs mainly target adolescents and young adults. However, several reports associate CED ingestion with serious caffeine intoxication [2, 13]. A recent analysis showed that approximately 80 % of non-alcoholic CED exposures reported to the US National Poison Data System occurred in children or adolescents [11]. Nevertheless, CEDs are still commonly sold without any legal restrictions in many areas. In our opinion, this is most likely due to the difficulty in demonstrating a causal relationship between CED ingestion and adverse events.

Serious caffeine intoxication syndrome includes hallucinations, seizures, metabolic acidosis, rhabdomyolysis, and arrhythmias [10]. Currently, no consensus exists regarding the cutoff values for plasma caffeine concentrations that may result in varying toxicities. While plasma caffeine concentrations of <10 mg/L are generally considered safe, those in fatal caffeine poisoning cases are usually reported as higher than 80 mg/L [3, 5, 6, 12]. Nonetheless, several fatalities of caffeine poisoning have also been documented with plasma caffeine concentrations of <40 mg/L [1, 2], and non-fatal toxicities can occur at much lower concentrations. Some investigators suggested that fairly low plasma caffeine concentrations of ≥15 mg/L can sometimes lead to toxicity [1].

The aim of this study is to investigate plasma caffeine concentration profiles expected after the ingestion of standard servings of CED in young adolescents and the associated risk of caffeine intoxication. Because it would not be ethically feasible to conduct an analysis regarding caffeine intoxication in human subjects following the administration of potentially toxic caffeine dosages, we instead performed an in silico pharmacokinetic analysis of caffeine consumption via Monte Carlo simulation.

Methods

Pharmacokinetic model of caffeine

This study employed a population pharmacokinetic model of oral caffeine derived from a study of 30 healthy adult male volunteers (mean age 24.0 years) of South Asian and European ancestry [8, 9]. The population pharmacokinetic analysis was performed using non-linear, mixed-effects modeling and NONMEM 7.3 ADVAN2 software (Icon Development Solutions, Ellicott City, MD, USA). A one-compartment pharmacokinetic model with first-order absorption/elimination kinetics was best fitted to the pharmacokinetic data, resulting in the following equation for the prediction of maximum plasma caffeine concentration (C_{max}) values and the time at which C_{max} is observed (t_{max}):

$$C_{max} = \frac{\text{Dose} \times k_a}{V(k_a - k_e)} \left(\exp(-k_e \times t_{max}) - \exp(-k_a \times t_{max})\right)$$

$$t_{max} = \frac{\ln(k_a) - \ln(k_e)}{(k_a - k_e)}$$

where k_a is the absorption rate constant, V is the volume of distribution, and k_e is the elimination rate constant.

The only covariate in the final model was body weight, which incorporated linearly, and it was better than other non-linearly combined models. The final model was internally validated. The final pharmacokinetic parameters were derived as follows:

$$CL\left(L/hr\right) = 0.09792 \times \text{body weight} \times \exp(\eta_1)$$

$$V(L) = 0.1105 \times \text{body weight} \times \exp(\eta_2)$$

$$k_a\left(/hr\right) = 4.268 \times \exp(\eta_3)$$

$$\begin{bmatrix} \eta_1 \\ \eta_2 \\ \eta_3 \end{bmatrix} \sim MVN\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0.1599 & 6.095 \times 10^{-2} & 9.650 \times 10^{-2} \\ 6.095 \times 10^{-2} & 4.746 \times 10^{-2} & 1.359 \times 10^{-2} \\ 9.650 \times 10^{-2} & 1.359 \times 10^{-2} & 1.004 \end{bmatrix} \right)$$

where CL is the clearance, η is the interindividual random variability parameter, and MVN is the multivariate normal distribution.

Body weight data

This study utilized the body weight data of young Korean adolescents, 10–15 years of age (http://www.cdc.go.kr/CDC/info/).

Table 1 Distributions of predicted maximum plasma caffeine concentration (C_{max}) values following caffeinated energy drink (CED) intake according to the amount of caffeine ingested and body weight

Amount of caffeine[a]	C_{max} (mg/L)	Body weight[b]													
		23 kg[c]	25 kg	30 kg	35 kg	40 kg	45 kg	50 kg	55 kg	60 kg	65 kg	70 kg	75 kg	80 kg	84 kg[d]
80 mg	Median	4.2	3.9	3.2	2.7	2.4	2.2	1.9	1.8	1.6	1.5	1.4	1.3	1.2	1.2
	25–75 %	3.5–5.0	3.3–4.5	2.7–3.8	2.4–3.2	2.1–2.8	1.8–2.5	1.6–2.3	1.5–2.1	1.4–1.9	1.3–1.7	1.2–1.6	1.1–1.5	1.0–1.4	1.0–1.3
	Range	1.3–9.2	1.3–8.5	1.1–7.0	1.1–6.2	0.9–5.2	0.8–4.9	0.5–4.3	0.6–3.4	0.7–3.6	0.6–3.9	0.6–2.8	0.4–3.1	0.4–2.5	0.5–2.6
160 mg	Median	8.4	7.8	6.4	5.5	4.8	4.3	3.9	3.5	3.2	3.0	2.8	2.6	2.4	2.3
	25–75 %	7.1–10.0	6.6–9.1	5.5–7.6	4.7–6.5	4.1–5.6	3.6–5.0	3.3–4.5	3.0–4.1	2.7–3.7	2.5–3.5	2.4–3.2	2.2–3.0	2.1–2.8	2.0–2.7
	Range	2.7–18.4	2.6–16.9	2.1–14.1	2.2–12.5	1.7–10.5	1.6–9.7	1.1–8.6	1.3–6.7	1.4–7.3	1.2–7.8	1.1–5.7	0.8–6.2	0.8–5.0	0.9–5.1
240 mg	Median	12.6	11.7	9.6	8.2	7.2	6.5	5.8	5.3	4.8	4.5	4.2	3.9	3.6	3.5
	25–75 %	10.6–15.0	9.8–13.6	8.2–11.3	7.1–9.7	6.2–8.4	5.5–7.6	4.9–6.8	4.5–6.2	4.1–5.6	3.8–5.2	3.6–4.9	3.3–4.6	3.1–4.2	2.9–4.0
	Range	4.0–27.6	3.9–25.4	3.2–21.1	3.3–18.7	2.6–15.7	2.4–14.6	1.6–12.9	1.9–10.1	2.0–10.9	1.7–11.8	1.7–8.5	1.2–9.3	1.2–7.5	1.4–7.7
320 mg	Median	16.8	15.6	12.9	11.0	9.7	8.6	7.7	7.0	6.4	6.0	5.6	5.1	4.8	4.6
	25–75 %	14.1–20.0	13.1–18.1	10.9–15.1	9.4–12.9	8.2–11.2	7.3–10.1	6.5–9.0	6.0–8.3	5.4–7.5	5.0–7.0	4.8–6.5	4.3–6.1	4.1–5.6	3.9–5.4
	Range	5.4–36.8	5.2–33.8	4.2–28.2	4.4–24.9	3.5–21.0	3.2–19.5	2.1–17.3	2.6–13.4	2.7–14.6	2.3–15.7	2.2–11.3	1.6–12.4	1.6–10.0	1.8–10.2
484 mg	Median	25.4	23.6	19.5	16.6	14.6	13.1	11.7	10.6	9.7	9.0	8.5	7.8	7.2	7.0
	25–75 %	21.4–30.2	19.8–27.4	16.5–22.9	14.3–19.5	12.4–17.0	11.0–15.2	9.9–13.7	9.1–12.5	8.2–11.3	7.6–10.6	7.2–9.8	6.6–9.2	6.2–8.5	5.9–8.1
	Range	8.1–55.6	7.8–51.2	6.4–42.6	6.7–37.7	5.3–31.7	4.8–29.5	3.2–26.1	3.9–20.3	4.1–22.0	3.5–23.7	3.3–17.2	2.4–18.7	2.4–15.1	2.7–15.5

[a] The simulated caffeine dosages were determined based on the amounts of caffeine contained in one or two servings of four popular CEDs

[b] Simulated numbers of adolescents=2000 per each body weight group

[c] This value represents the third percentile of the body weight range for 10-year-old females

[d] This value represents the 97th percentile of the body weight range for 15-year-old males

Table 2 Distributions of predicted area under the curve (AUC) values following caffeinated energy drink (CED) intake according to the amount of caffeine ingested and body weight

Amount of caffeine[a]	AUC (mg/h/L)	Body weight[b]													
		23 kg[c]	25 kg	30 kg	35 kg	40 kg	45 kg	50 kg	55 kg	60 kg	65 kg	70 kg	75 kg	80 kg	84 kg[d]
80 mg	Median	35.0	32.5	27.4	22.9	20.2	18.1	16.2	14.7	13.4	12.8	11.9	10.8	10.0	9.8
	25–75 %	27.3–46.4	24.9-42.9	20.7-35.9	17.7-30.8	15.8-26.3	13.9-23.7	12.6-20.7	11.4-19.4	10.1-17.8	9.8-16.5	9.2-15.5	8.3-14.2	7.6-13.2	7.4-12.6
	Range	9.7–153.7	9.4-148.2	7.3–108.9	26.0-504.6	6.3-74.1	4.6-79.2	3.6-55.2	3.9-51.5	2.9-44.8	3.9-46.7	2.9-40.9	3.1-38.9	3.0-36.0	2.6-40.7
160 mg	Median	70.0	64.9	54.8	45.8	40.4	36.2	32.4	29.4	26.8	25.6	23.8	21.6	20.0	19.6
	25–75 %	54.6–92.8	49.8-85.8	41.4–71.8	35.4-61.6	31.6-52.6	27.8-47.4	25.2-41.4	22.8-38.8	20.3-35.6	19.6-33.0	18.4-31.0	16.6-28.4	15.3-26.4	14.8-25.2
	Range	19.4–307.4	18.8–296.4	14.6-217.8	8.6-166.8	12.6-148.2	9.2-158.4	7.2-110.4	7.8-103.0	5.8-89.6	7.8-93.4	5.8-81.8	3.1-38.9	6.0-72.0	5.2-81.4
240 mg	Median	105.0	97.4	82.2	68.7	60.6	54.3	48.6	44.1	40.2	38.4	35.7	32.4	30.0	29.4
	25–75 %	81.9–139.2	74.7-128.7	62.1-107.7	53.1-92.4	47.4-78.9	41.7-71.1	37.8-62.1	34.2-58.2	30.4-53.4	29.4-49.5	27.6-46.5	24.9-42.6	22.9-39.6	22.2-37.8
	Range	29.1–461.1	28.2-444.6	21.9-326.7	26.0-504.6	18.9-222.3	13.8-237.6	10.8-165.6	11.7-154.5	8.7-134.4	11.7–140.1	8.7–122.7	9.3-116.7	9.0-108.0	7.8-122.1
320 mg	Median	140.0	129.8	109.6	91.6	80.8	72.4	64.8	58.8	53.6	51.2	47.6	43.2	40.0	39.2
	25–75 %	109.2–185.6	99.6-171.6	82.8-143.6	70.8-123.2	63.2-105.2	55.6-94.8	50.4-82.8	45.6-77.6	40.5-71.2	39.2-66.0	36.8-62.0	33.2-56.8	30.5-52.8	29.6-50.4
	Range	38.8–614.8	37.6-592.8	29.2-435.6	17.2-333.6	25.2-296.4	18.4-316.8	14.4-220.8	15.6-206.0	11.6-179.2	15.6-186.8	11.6-163.6	12.4-155.6	12.0-144.0	10.4-162.8
484 mg	Median	211.8	196.3	165.8	138.5	122.2	109.5	98.0	88.9	81.1	77.4	72.0	65.3	60.5	59.3
	25–75 %	165.2–280.7	150.6-259.5	125.2–217.2	107.1-186.3	95.6-159.1	84.1-143.4	76.2-125.2	69.0-117.4	61.3-107.7	59.3–99.8	55.7-93.8	50.2-85.9	46.1-79.9	44.8-76.2
	Range	58.7–929.9	56.9-896.6	44.2-658.8	26.0-504.6	38.1-448.3	27.8-479.2	21.8-334.0	23.6-311.6	17.5-271.0	23.6-282.5	17.5-247.4	18.8-235.3	18.2-217.8	15.7-246.2

[a] The simulated caffeine dosages were determined based on the amounts of caffeine contained in one or two servings of four popular CEDs

[b] Simulated numbers of adolescents=2000 per each body weight group

[c] This value represents the third percentile of the body weight range for 10-year-old females

[d] This value represents the 97th percentile of the body weight range for 15-year-old males

Table 3 Distributions of predicted maximum plasma caffeine concentration (C_{max}) values following caffeinated energy drink (CED) intake according to the amount of caffeine ingested and age/gender

		Age 10–11 years[b]			Age 11–12 years[b]			Age 12–13 years[b]			Age 13–14 years[b]			Age 14–15 years[b]		
Amount of caffeine[a]	C_{max} (mg/L)	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
80 mg	Median	2.8	2.7	2.7	2.5	2.4	2.4	2.2	2.1	2.2	2.0	1.9	2.0	1.9	1.7	1.8
	25–75 %	2.2–3.4	2.2–3.4	2.2–3.4	2.0–3.0	1.9–2.9	2.0–3.0	1.8–2.7	1.7–2.6	1.8–2.7	1.6–2.5	1.5–2.3	1.6–2.4	1.5–2.3	1.4–2.1	1.5–2.2
	Range	0.9–6.8	0.8–7.2	0.8–7.2	0.8–5.9	0.7–7.1	0.7–7.1	0.6–5.0	0.6–5.7	0.6–5.7	0.6–5.6	0.6–5.4	0.6–5.6	0.6–5.3	0.6–4.7	0.6–5.3
160 mg	Median	5.6	5.3	5.5	4.9	4.8	4.8	4.4	4.3	4.3	4.0	3.8	3.9	3.7	3.5	3.6
	25–75 %	4.5–6.9	4.3–6.7	4.4–6.8	4.0–6.0	3.9–5.8	3.9–5.9	3.6–5.4	3.4–5.2	3.5–5.3	3.3–4.9	3.1–4.7	3.2–4.8	3.1–4.5	2.8–4.2	3.0–4.4
	Range	1.9–13.6	1.6–14.3	1.6–14.3	1.6–11.8	1.3–14.2	1.3–14.2	1.1–10.0	1.3–11.4	1.1–11.4	1.2–11.2	1.1–10.8	1.1–11.2	1.3–10.7	1.2–9.3	1.2–10.7
240 mg	Median	8.4	8.0	8.2	7.4	7.2	7.3	6.6	6.4	6.5	6.0	5.7	5.9	5.6	5.2	5.4
	25–75 %	6.7–10.3	6.5–10.1	6.6–10.2	6.0–9.0	5.8–8.7	5.9–8.9	5.4–8.1	5.2–7.8	5.3–8.0	4.9–7.4	4.6–7.0	4.8–7.2	4.6–6.8	4.2–6.4	4.4–6.6
	Range	2.8–20.4	2.5–21.5	2.5–21.5	2.4–17.7	2.0–21.3	2.0–21.3	1.7–14.9	1.9–17.1	1.7–17.1	1.7–16.8	1.7–16.3	1.7–16.8	1.9–16.0	1.8–14.0	1.8–16.0
320 mg	Median	11.2	10.6	11.0	9.8	9.6	9.7	8.8	8.6	8.7	8.0	7.6	7.8	7.5	6.9	7.2
	25–75 %	9.0–13.8	8.6–13.5	8.8–13.6	8.0–12.0	7.7–11.6	7.8–11.8	7.2–10.7	6.9–10.4	7.0–10.6	6.6–9.8	6.1–9.3	6.4–9.5	6.2–9.1	5.6–8.5	5.9–8.8
	Range	3.8–27.3	3.3–28.7	3.3–28.7	3.2–23.6	2.6–28.4	2.6–28.4	2.3–19.9	2.6–22.8	2.3–22.8	2.3–22.3	2.3–21.7	2.3–22.3	2.5–21.3	2.4–18.7	2.4–21.3
484 mg	Median	16.9	16.1	16.6	14.9	14.5	14.7	13.3	13.0	13.1	12.1	11.5	11.8	11.3	10.5	10.9
	25–75 %	13.6–20.8	13.0–20.4	13.3–20.6	12.1–18.2	11.7–17.5	11.8–17.9	10.9–16.3	10.4–15.8	10.6–16.0	9.9–14.8	9.3–14.1	9.7–14.4	9.3–13.7	8.4–12.8	8.9–13.3
	Range	5.7–41.2	5.0–43.4	5.0–43.4	4.8–35.7	4.0–43.0	4.0–43.0	3.5–30.1	3.9–34.5	3.5–34.5	3.5–33.8	3.4–32.8	3.4–33.8	3.8–32.2	3.6–28.3	3.6–32.2

[a] The simulated caffeine dosages were determined based on the amounts of caffeine contained in one or two servings of four popular caffeinated energy drinks (CEDs)

[b] Simulated numbers of adolescents=2000 per each age/gender group

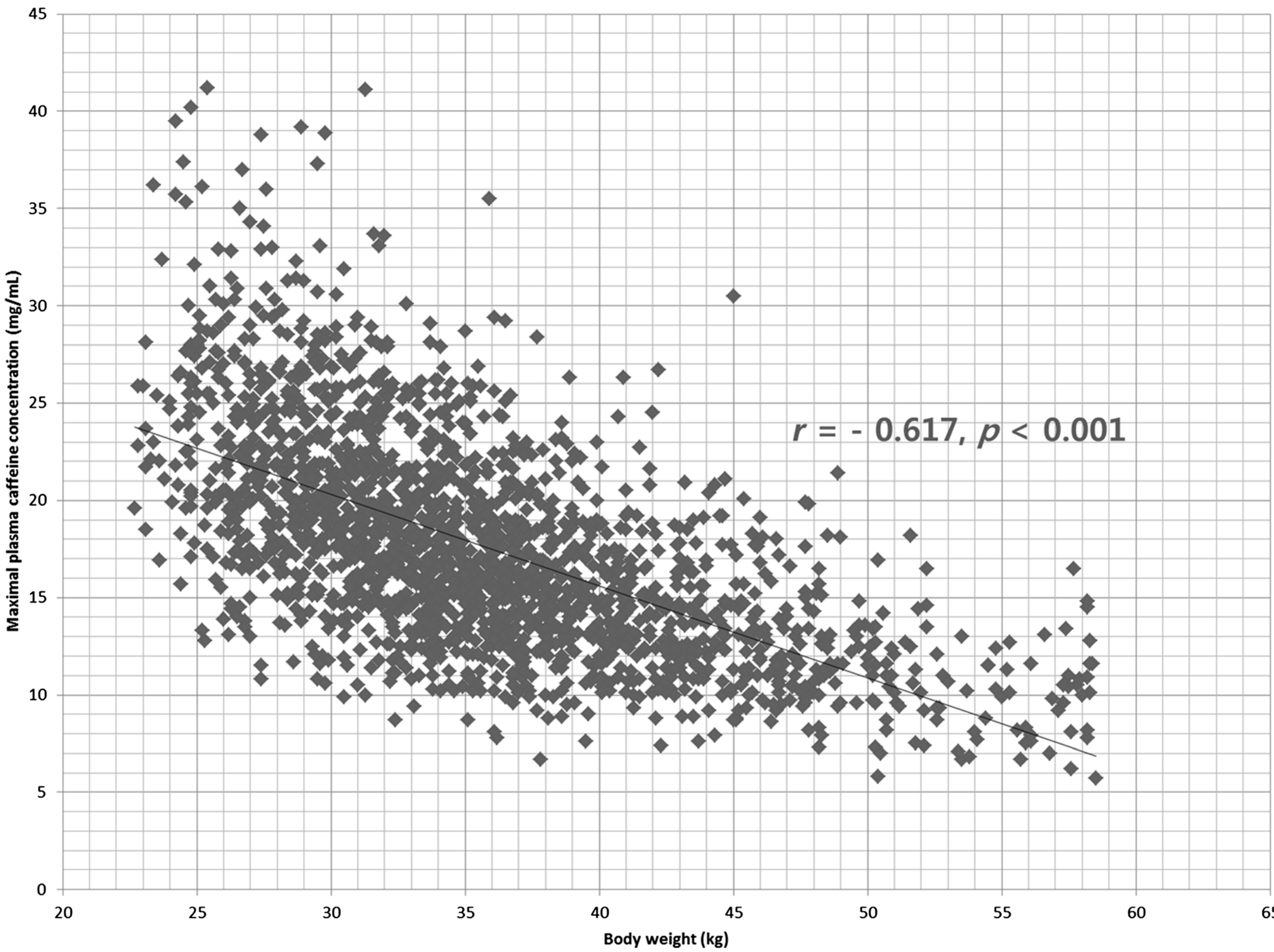

Fig. 1 Correlation between C_{max} values and body weight in the 10–11-year-old female group following ingestion of 484 mg caffeine from caffeine-containing energy drinks

Monte Carlo simulation

Monte Carlo simulation is a problem solving technique that relies on random sampling and statistical modeling to determine the probability of certain outcomes. It is most useful when experimentation is too time-consuming, costly, or impractical to perform [4]. Monte Carlo simulation was performed by using the final population model parameters and NONMEM software. The final model was chosen based on goodness of fit and objective function value. Individual C_{max} profiles following CED-mediated intake of 80, 160, 240, 320, or 484 mg caffeine were simulated based on caffeine content in one or two servings of four popular CEDs (Red Bull®, 80 mg; Monster® and Rockstar®, 160 mg; 5 h Energy Extra Strength®, 242 mg). Each Monte Carlo simulation generated C_{max} profiles for 2000 subjects per each body weight group (body weight=23–84 kg, divided into groups of 23, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, and 84 kg) and age/gender group (age/gender=10–11-, 11–12-, 12–13-, 13–14-, and 14–15-year-old male or female subjects). Correlations between the pharmacokinetic variables, CL, V, and k_a, were reflected in the simulation by using the variance-covariance matrix generated from the estimation. An exemption was granted by the Institutional Review Board.

Results

Predicted C_{max} values after CED intake according to the amount of caffeine ingested and body weight

The distributions of simulated caffeine C_{max} and area under the curve (AUC) values following the ingestion of CEDs were stratified according to body weight and the amount of caffeine intake and are shown in Tables 1 and 2, respectively. With an initial caffeine intake of 80 mg, the median C_{max} value varied from a low of 1.2 (range, 0.5–2.6) mg/L to a high of 4.2 (range, 1.3–9.2) mg/L. The median C_{max} values across all body weight groups varied from 2.3 to 8.4 (range, 0.9–18.4) mg/L after a caffeine intake of 160 mg, 3.5 to 12.6 (range 1.4–27.6) mg/L after a caffeine intake of 240 mg, and 4.6 to 16.8 (range, 1.8–36.8) mg/L after a caffeine intake of 320 mg. With 484 mg of ingested caffeine, the median C_{max} values varied from 7.0 (range, 2.7–15.5) to 25.4 (range, 8.1–55.6) mg/L.

Predicted C_{max}values after CED intake according to the amount of caffeine ingested and age/gender

Table 3 shows the distributions of simulated C_{max} values according to age/gender and the amount of caffeine intake. The 10–11-year-old female group exhibited the highest C_{max} profiles, with a median C_{max} value that varied from 2.8 (range, 0.9–6.8) to 16.9 (range, 5.7–41.2) mg/L. On the other hand, the 14–15-year-old male group exhibited the lowest C_{max} profiles, with a median C_{max} value varying from 1.7 (range, 0.6–4.7) to 10.5 (range, 3.6–28.3). There was strong negative correlation between C_{max} values and body weight (Pearson's correlation coefficient, r=−787, p<0.001). Figure 1 shows exemplified correlation between C_{max} values and body weight in the 10–11-year-old female group following ingestion of 484 mg of caffeine from caffeine-containing energy drinks (Pearson's correlation coefficient, r=−0.617, p<0.001).

Discussion

Currently available data concerning plasma caffeine concentrations are mainly derived from reports of severe caffeine intoxication after ingestion of very large caffeine doses of the compound, or from the limited number of studies testing relatively small dosages in healthy adult volunteers. However, little information is available regarding caffeine-related harms in adolescents.

Without an evident history of the overusage of caffeinated products, most physicians would not initially consider the possibility of caffeine intoxication syndrome in their clinical practice. Therefore, the incidence of this malady may have been underestimated in the past. In the present analysis, caffeine C_{max} profiles varied widely according caffeine intake and body weight of the subjects. Surprisingly, the C_{max} profiles of adolescents with lower body weights showed an overlap with the ingested caffeine concentrations obtained from documented fatalities. These observations might suggest that popular CEDs are associated with a risk of serious caffeine intoxication in young adolescents.

Several points must be emphasized while interpreting our results. First, although the caffeine C_{max} profiles were <10 mg/L in all age groups for subjects who consumed 80 mg of caffeine, this finding does not signify that CEDs containing ≤80 mg of caffeine are safe. In the present study, we utilized data acquired in the absence of caffeine intake for at least 24 h. Therefore, the recent daily consumption of caffeine was not taken into account, and the actual C_{max} of caffeine might have been considerably higher. Second, because most CEDs are packaged in relatively small volumes of 57–250 mL, young users of these beverages frequently consume two or more servings over a short period of time [7]. This pattern of consumption can rapidly lead to high plasma concentrations of caffeine. Third, similar plasma caffeine concentrations may exert more pronounced effects in persons with vulnerable conditions, such as an underlying seizure disorder or a cardiovascular disorder. These at-higher-risk populations will probably require lower cutoff values of caffeine to avoid serious adverse events.

The present study has several limitations. First, our main subjects were adolescents of both sexes. However, the equations employed for the analysis were generated from data corresponding to a healthy adult male population. Therefore, the findings may not be entirely applicable to adolescents or female subjects. There may be differences in caffeine absorption and metabolism between males and females. Second, the current investigation focused only on caffeine and, therefore, the possibility cannot be ruled out that other CED ingredients, such as taurine, impacted the results. Third, the study was based on extensive sampling of a small population of healthy volunteers with similar characteristics. Therefore, the application of covariate analysis was not possible. Finally, CYP1A2 polymorphisms and impact of chronic caffeine exposure, which could influence caffeine metabolism, were not evaluated.

In conclusion, this study demonstrated that plasma caffeine concentrations can be sufficiently high in young adolescents after CED ingestion to cause serious caffeine intoxication. Our data are in support of the need for a prospective clinical study. The toxic range of plasma caffeine concentration should also be determined.

Conflict of interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Contribution of authors Jung Woo Lee: study conception and design, and drafting the manuscript.

Yoo Kyung Kim: study conception and design, and revising the manuscript critically for important intellectual content.

Vidya Perera: Data acquisition and analysis, and revising the manuscript critically for important intellectual content.

Andrew J McLachlan: Data acquisition and analysis, and revising the manuscript critically for important intellectual content.

Kyun-Seop Bae: Study conception and design, data analysis and interpretation, and revising the manuscript critically for important intellectual content.

References

1. Banerjee P, Ali Z, Levine B, Fowler DR (2014) Fatal caffeine intoxication: a series of eight cases from 1999 to 2009. J Forensic Sci 59:865–868
2. Cannon ME, Cooke CT, McCarthy JS (2001) Caffeine-induced cardiac arrhythmia: an unrecognised danger of healthfood products. Med J Aust 174:520–521
3. de Wijkerslooth LR, Koch BC, Malingre MM, Smits P, Bartelink AK (2008) Life-threatening hypokalaemia and lactate accumulation after autointoxication with stacker 2, a ‘powerful slimming agent’. Br J Clin Pharmacol 66:728–731
4. Harrison RL (2010) Introduction to Monte Carlo simulation. AIP Conf Proc 1204:17–21
5. Holmgren P, Norden-Pettersson L, Ahlner J (2004) Caffeine fatalities–four case reports. Forensic Sci Int 139:71–73
6. Kerrigan S, Lindsey T (2005) Fatal caffeine overdose: two case reports. Forensic Sci Int 153:67–69
7. Malinauskas BM, Aeby VG, Overton RF, Carpenter-Aeby T, Barber-Heidal K (2007) A survey of energy drink consumption patterns among college students. Nutr J 6:35
8. Perera V, Gross AS, Forrest A, Landersdorfer CB, Xu H, Ait-Oudhia S, McLachlan AJ (2013) A pharmacometric approach to investigate the impact of methylxanthine abstinence and caffeine consumption on CYP1A2 activity. Drug Metab Dispos Biol Fate Chem 41:1957–1966
9. Perera V, Gross AS, Xu H, McLachlan AJ (2011) Pharmacokinetics of caffeine in plasma and saliva, and the influence of caffeine abstinence on CYP1A2 metrics. J Pharm Pharmacol 63:1161–1168
10. Seifert SM, Schaechter JL, Hershorin ER, Lipshultz SE (2011) Health effects of energy drinks on children, adolescents, and young adults. Pediatrics 127:511–528
11. Seifert SM, Seifert SA, Schaechter JL, Bronstein AC, Benson BE, Hershorin ER, Arheart KL, Franco VI, Lipshultz SE (2013) An analysis of energy-drink toxicity in the national poison data system. Clin Toxicol 51:566–574
12. Thelander G, Jonsson AK, Personne M, Forsberg GS, Lundqvist KM, Ahlner J (2010) Caffeine fatalities–do sales restrictions prevent intentional intoxications? Clin Toxicol 48:354–358
13. Trabulo D, Marques S, Pedroso E (2011) Caffeinated energy drink intoxication. BMJ Case Rep. doi:10.1136/bcr.09.2010.3322