A Retrospective Study of Clinical Effects of Powdered Caffeine Exposures Reported to Three US Poison Control Centers.

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Published In/Presented At

Beauchamp GA, Johnson AR, Crouch BI, Valento M, Horowitz BZ, Hendrickson RG. A Retrospective Study of Clinical Effects of Powdered Caffeine Exposures Reported to Three US Poison Control Centers. J Med Toxicol. 2016 Sep;12(3):295-300. doi: 10.1007/s13181-016-0545-9.

J. Med. Toxicol. (2016) 12:295–300
DOI 10.1007/s13181-016-0545-9

ORIGINAL ARTICLE

A Retrospective Study of Clinical Effects of Powdered Caffeine Exposures Reported to Three US Poison Control Centers

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Received: 24 November 2015 / Revised: 11 February 2016 / Accepted: 21 March 2016 / Published online: 4 April 2016

Abstract
Introduction Anhydrous caffeine, often sold on the Internet as a powdered caffeine product, is sold as "pure caffeine" to be used as an additive to beverages and has also been used as an ingredient in energy supplement products.
Methods This is a retrospective multiple-poison center chart review of calls regarding powdered caffeine to poison centers covering Oregon, Alaska, Guam, Washington, and Utah between January 1, 2013 and June 30, 2015.
Results There were 40 calls to three poison centers over 30 months for powdered caffeine exposure. The majority of patients were over age 19 (52.5 %; 21/40) and male (70 %; 28/40). Sixty percent (24/40) of the patients were symptomatic but only 10 % (4/40) required admission; 52.5 % (21/40) of the patient calls were for inadvertent overdose of powdered caffeine; one patient overdosed in a self-harm attempt.
Discussion Powdered caffeine calls to three poison centers during a 30-month study period were rare, and severe caffeine toxicity due to exposure was found in few patients. The majority of symptoms were reported after an inadvertent powdered caffeine overdose.
Conclusions An analysis of calls to three poison centers for powdered caffeine found that exposures were uncommon, but did result in toxicity, and highlighted that the lack of clear dosing instructions on product packaging may place patients at risk of inadvertent overdose.

Keywords Powdered caffeine · Dietary supplement · Poison center

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Introduction

Caffeine (1,3,7-trimethylxanthine) is ingested for its stimulant effects in caffeinated beverages and in products marketed to enhance physical and mental performance and energy [1–5]. Caffeinated beverages are known to cause severe toxicity when consumed in excess [6–18]. Dietary supplements that may contain botanical or synthetic caffeine have also produced toxicity in patients, particularly when multiple caffeinated or other stimulant products are used concomitantly, or when products are used in conjunction with physical exertion [19–28].

Anhydrous caffeine is sold as a powdered caffeine product to be used as an additive to beverages. Caffeine has also been used as an ingredient in energy supplement products, commonly ingested beverages, and over-the-counter stimulant medications [21, 27, 28]. Caffeine is rapidly absorbed with a peak plasma concentration within 60 min and has caused fatal overdoses at estimated doses of 150 mg/kg [29–32]. Severe toxicity from caffeine exposure may result from catecholamine release resulting in sympathetic overdrive, seizures, and tachydysrhythmias [1, 33, 34]. While caffeine-containing supplements are not regulated by the Food and Drug Administration, a warning regarding powdered caffeine toxicity was released in December 2014 stating that

one teaspoon of a powdered caffeine product could have the equivalent of "about 25 cups of coffee" [35]. Unregulated supplement products have potential to cause harm in users due to lack of available research on appropriate dosing and effects.

Poison centers manage calls from individual consumers as well as medical providers caring for patients with potential poisonings. Our objective was to examine calls regarding powdered caffeine to a convenience sample of poison centers covering Oregon, Alaska, Guam, Utah, and Washington to determine demographics of exposures, reason for ingestion, amount ingested, effects, and outcomes. This initial retrospective case review was performed in order to further understand the complications of these products and to guide the timely development of management protocols and prevention measures for powdered caffeine toxicity.

Methods

IRB approval was obtained by each of the participating poison centers. This was a retrospective multiple-poison center chart review using a convenience sample of 30 months of potential exposures to powdered caffeine reported to poison centers covering Oregon, Alaska, Guam, Washington, and Utah, from January 1, 2013 through June 30, 2015. Over the 30-month study time period, poison center medical records for exposures to powdered caffeine were reviewed. To ensure a thorough review of potential powdered caffeine exposures, the search terms used included "Diet Aid: Phenylpropanolamine and Caffeine," "Energy Drinks: Ethanol and Caffeine Containing; Energy Drinks: Caffeine Containing," "Energy Drinks: Caffeine only," "Caffeine," "Powdered Caffeine," and "Anhydrous Caffeine." A single study investigator screened charts identified using this search strategy and included charts if the call was regarding a powdered caffeine product. Charts were excluded from the study if the exposure of concern involved another form of caffeine such as caffeine pills, energy drinks, or other caffeine supplement. The call charts were then reviewed for origin of call (state), age, gender, description of exposure, product name, amount ingested when known, signs and symptoms, treatment provided, and disposition. Chart abstraction was performed by two study investigators who were blinded to the other's abstraction. A third study investigator reviewed the dual abstraction spreadsheets for discrepancies. A study biostatistician calculated Cohen's kappa and corresponding 95 % confidence intervals (CI) to measure interrater reliability [36]. For dichotomous variables, the analytic method was used to calculate the 95 % CI and for variables with more than two levels, the bootstrap method was used [37]. Descriptive statistics were used to provide summary data including mean age, percentage of exposures by gender, and percentage of exposures with symptoms requiring treatment.

Results

A retrospective chart review of calls regarding powdered caffeine to Oregon, Alaska, Guam, Utah, and Washington poison centers over a 30-month period revealed 40 reported powdered caffeine exposures. See Table 1 for number of calls for potential powdered caffeine exposure by study state, as well as total number of calls to study poison centers during the study time period, and estimated state populations. The National Poison Data System, which collects summary data from all national poison centers (covering an estimated 2014 US Census Bureau total US population of 318,857,056) noted a total of 5,431,050 exposure calls during the study time period. The 390,597 total exposure calls received by the participating centers represented 7 % of this national call volume during the study time period. A total of 802 charts were reviewed across three poison centers: Utah, 318 charts reviewed and 298 excluded; Oregon, Alaska, and Guam, 221 charts reviewed and 212 excluded; and Washington, 263 reviewed and 252 excluded. See Table 2 for patient demographics and reason for call to poison center. Most patients were male (70 %; 28/40) and slightly more than half were over 19 years of age (52.5 %; 21/40). See Table 3 for patient symptoms, signs, treatments, and outcomes. Most calls were regarding patients who were symptomatic at the time of the call (60 %; 24/40), and

Table 1 Calls to poison centers for powdered caffeine by state versus total poison center exposure calls and estimated state population

State	Number	Percent of all study calls (%)	Total exposure calls to poison center by state[a]	Estimated state population during study[b]
Oregon	8	20	109,240	3,970,239
Alaska	1	2.5	20,100	736,732
Washington	11	28	159,756	7,061,530
Utah	20	50	101,501	2,942,902

[a] Total exposure calls to poison centers based on American Association of Poison Control Centers National Poison Data System data

[b] State populations based on 2014 United States Census Bureau Estimates. Available at http://quickfacts.census.gov/qfd/states/41000.html. Accessed January 2, 2016

Table 2 Demographics and reason for call for powdered caffeine exposures reported to three US poison control centers

Demographics	Number	Percent of all study calls (%)
Age 0–5	14	35%
Age 6–12	2	5
Age 13–19	3	7.5
Age over 19	21	52.5
Females	12	30
Males	28	70
Reason for call		
Symptomatic	24	60
Dosing question	1	2.5
Adult inadvertent overdose	21	52.5
Self-harm attempt	1	2.5
Possible pediatric exposure	16	40

Table 3 Symptoms, signs, treatment, and outcomes for powdered caffeine exposures reported to three US poison control centers

	Number	Percent of all study calls (%)
Symptoms		
Nausea or vomiting	17	42.5
Diarrhea	1	2.5
Lightheaded or weak	6	15
Anxious or hyperactive	11	27.5
Tremulous	3	7.5
Muscle spasm	1	2.5
Chest pain	4	10
Palpitations	9	22.5
Signs		
Tachycardia	11	27.5
Hypertension	4	10
Hypotension	2	5
Arrhythmia	3	7.5
Tachypnea	1	2.5
Treatment		
Intravenous fluids	7	17.5
Benzodiazepines	7	17.5
Beta blockers	2	5
Anti-emetics	5	12.5
Potassium repletion	3	7.5
Disposition		
Remained at home	28	70
ED evaluation with discharge	8	20
Admit to floor bed	1	2.5
Admit to intensive care unit (ICU)	3	7.5

more than half of patients were symptomatic adults who reported an inadvertent overdose due to lack of dosing information on the product packaging (52.5 %; 21/40). Of 14 patients in the age 0–5 years age group, four were reported to be symptomatic (29 %; 4/14). Of two patients in the age 6–12 age group, none became symptomatic. All three patients in the age 13–19 age group were described as symptomatic (100 %, 3/3).

Of patients evaluated by a medical professional, 27.5 % (11/40) had tachycardia which ranged from 100 to 200 beats per minute; 10 % (4/40) had hypertension for which systolic blood pressures ranged from 140 to 171 mmHg; and two patients (5 %; 2/40) had hypotension with a range in systolic blood pressure of 70-108 mmHg Of the three patients who had dysrhythmias, one had atrial fibrillation, one had frequent premature ventricular complexes, and one had bigeminy. Treatment provided included intravenous fluids, benzodiazepines, anti-emetics, beta blockers, and potassium repletion.

As examples of severe toxicity, the three patients admitted to the ICU are described here. A 70-year-old male who took a “tablespoon” of powdered caffeine for an unknown reason, presented with tachycardia, hypertension, and hypokalemia. A 27-year-old male with an estimated 9-g powdered caffeine ingestion taken to “stay awake” resulted in tachycardia, hypotension, chest pain, nausea, and vomiting managed with adenosine, esmolol, lorazepam, and diazepam. The third patient was a 48-year-old female who reportedly ingested “100 g” of powdered caffeine contained in a “packet” in a self-harm attempt. She developed atrial fibrillation with rapid ventricular response, hypotension, agitation, tremor, metabolic acidosis, and hypokalemia, which was managed with intravenous fluids, midazolam infusion, potassium repletion, esmolol infusion, anti-emetics, and lorazepam boluses.

Most patients managed by these poison centers remained at home (70 %; 28/40), including all 16 patients aged 0–12 years, none of the three patients aged 13–19 years, and 12 of the 21 patients over the age of 19 years. Of the 12 patients who received medical care, one third were admitted to the hospital. There were no deaths reported. Among the 17 symptomatic adult patients, 16 patients had inadvertent overdosing during non-self-harm ingestions (94 %; 16/17). These overdoses reportedly occurred due to lack of dosing instructions on packaging and resulted in a range of reported ingestions from 100 mg to 9 g. One self-harm ingestion reportedly involved a 100-g ingestion.

Among the 14 pediatric exposures in the age 0–5 years age group, all were accidental ingestions of beverages to which powdered caffeine had been added. All remained asymptomatic except for four patients: a 3-year-old female with maximum possible ingestion of 100 mg was described by the caller as “hyperactive”; a 5-year-old male with a maximum ingestion of 120 mg developed nausea; a 2-year-old female with

maximum ingestion of 135 mg was described by the caller as "jittery"; and a 10-month-old was described as having one bout of diarrhea after an accidental "sip" of a beverage to which an "unknown" amount of powdered caffeine had been added. All four of these symptomatic pediatric patients were kept at home with subsequent poison center follow-up calls with eventual resolution of patients' symptoms. The two patients in the age 6–12 years age range remained asymptomatic after the accidental ingestion of beverages to which powdered caffeine had been added. All calls regarding pediatric exposures in the age 0–12 years age group were described as accidental exposures involving the consumption of a beverage to which another individual had added powdered caffeine. All calls regarding potential ingestions in individuals age 13 years and older involved the ingestion of beverages to which the subject of the call had self-administered powdered caffeine. These included three teenagers who developed symptoms after non-self-harm ingestions of beverages to which they had added powdered caffeine: a 17-year-old female developed premature ventricular contractions, a 17-year-old male developed vomiting and weakness, and a 15-year-old male developed tachycardia and nausea. All three patients were treated and discharged from the emergency department.

Interrater reliability was excellent with a kappa being 0.95 or above for all 27 study characteristics.

Discussion

Powdered caffeine calls to three poison centers during a 30-month study period were rare, and severe caffeine toxicity due to exposure was found in few patients. The majority of concerns from individual consumers surrounded symptoms reported after an inadvertent powdered caffeine overdose. A recent laboratory analysis of powdered caffeine products purchased from the Internet revealed a consistent lack of clear instructions for dosing, as well as high purity (median 90 % purity) [38]. Inadvertent overdose in this poison center retrospective chart review was reported by over half of callers. Given that the powdered caffeine dose equivalent to a cup of caffeinated coffee beverage is estimated to be 1/28–1/32 of a standard measuring teaspoon, lack of dosing instructions may place patients at risk for overuse [38].

Appropriate labeling of powdered caffeine products with accurate dosing instructions, including instructions on how to measure the product for consumption, has potential to prevent inadvertent overdose. In addition, warning labels educating consumers that combining highly concentrated caffeine products with other stimulants, particularly when consumed in conjunction with physical activity, may also help prevent adverse effects such as cardiotoxicity [21, 24–28, 39–44]. However, given the current lack of regulation of these products, appropriate labeling and product warnings may remain scarce. Therefore, providers should also be aware of the risks that accompany the ingestion of even small amounts of this product, as well as common presenting features of exposure to powdered caffeine, so that patients may be adequately educated and treated.

This small study revealed that pediatric patients aged 0–12 years with a potential or known ingestion of a small amount of beverage to which powdered caffeine had been added by another individual were able to be watched at home with phone follow-up by a poison center specialist. In patients older than age 12 years, symptoms were most commonly reported when they ingested a beverage to which powdered caffeine had been self-administered. While further studies are needed to guide the development of poison center protocols surrounding the management of powdered caffeine exposures, it may be possible to consider recommending home observation for accidental, low-dose pediatric exposures to mixed beverages, while teenage and adult exposures to larger amounts of powdered caffeine may require health-care facility referral.

There are a number of significant limitations to this study. Poison centers rely on data and information reported by callers, including type of exposure, doses, signs, and symptoms, which cannot typically be confirmed for accuracy [45]. No patients in this study had confirmatory caffeine concentration testing, so exposure to anhydrous caffeine was not confirmed in any of the 40 patients. This study assessed calls to a convenience sample of poison centers in the Western United States, and the results may not be applicable to other areas of the country or world. Despite this limitation, and the additional limitation that calls regarding powdered caffeine were rare, it might be expected that other poison centers would have received similar numbers of such exposure calls during the study time period. Abstraction of poison center charts, despite the use of dual abstraction with a third chart reviewer, may still have resulted in bias or abstraction error and therefore incorrect study conclusions. Finally, this study was limited by retrospective study design including lack of specific abstractor training, abstractor monitoring, and abstractor blinding to study hypothesis [46].

This study represents an initial assessment of powdered caffeine exposures reported to three poison centers serving four states and one US territory. As this is a relatively new and potentially dangerous product, further studies are needed to elucidate what effects may be experienced by patients with severe toxicity and what management steps are appropriate in the care of symptomatic powdered caffeine exposure patients. Prospective studies are needed to gather further data on the effects of powdered caffeine ingestion, including studies of patients treated in health-care facilities with confirmatory laboratory testing. The FDA sent warning letters to powdered caffeine distributors in September 2015 stating concern that the difference between a safe dose and toxic dose of this substance is very small, that safe quantities are nearly

impossible to measure using common kitchen measuring devices, and that the FDA would continue to aggressively monitor the marketplace for these products [47]. How these FDA statements will affect consumer use, overdoses, and poison center calls requires further study.

Conclusions

In conclusion, a retrospective chart review of exposures reported to three poison centers regarding powdered caffeine found that exposures rarely resulted in toxicity, but highlighted a lack of clear dosing instructions on product packaging, which may place patients at risk of inadvertent overdose.

Acknowledgments The authors would like to acknowledge Amber Laurie for her contributions as study biostatistician.

Compliance with Ethical Standards IRB approval was obtained by each of the participating poison centers.

Conflicts of Interest None

Sources of Funding None

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