Caffeine Toxicity: A Brief Review and Update.

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Published In/Presented At

Beauchamp, G. A., Amaducci, A. Cook, M. D. (2017). Caffeine Toxicity: A Brief Review and Update. *Clinical Pediatric Emergency and Update.18(3): 197-202.* https://doi.org/10.1016/j.cpem.2017.07.002

Abstract:
Caffeine is one of the most widely consumed psychoactive compounds and is often marketed for its physical and cognitive performance benefits. The ingestion of potentially toxic amounts of caffeine in the forms of energy drinks, over-the-counter supplements, or anhydrous caffeine products places vulnerable pediatric and adolescent individuals at risk for accidental overdose, resulting in neurologic and cardiac toxicity.

Keywords:
caffeine toxicity; pediatric emergency medicine; pediatrics; emergency medicine

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1522-8401

Caffeine Toxicity: A Brief Review and Update

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Caffeine, formally 1,3,7-trimethylxanthine, is one of the most widely consumed self-administered psychoactive compounds. Given its known stimulant effects, it is commonly used to enhance mental or physical performance.[1-6] Caffeine is an adenosine antagonist that is absorbed rapidly after ingestion, reaching peak effect within 30 minutes. Both desired and adverse effects occur via increased sympathomimetic activity and modulation of dopaminergic activity.[6] Although generally safe when consumed in moderation, caffeine may be tempting to consume in excess, which increases risk of significant toxicity. Caffeine is often ingested in pursuit of performance benefits such as improved physical endurance, weight loss, cognitive alertness, and reduction of perceived fatigue.[7] One survey determined that 80.1% of student athletes reported using energy drinks and 64.1% reported using dietary supplements to enhance athletic performance within the prior year.[8] The purpose of this review is to provide an overview and update of the recent literature on caffeine toxicity, with a specific focus on the pediatric population.

CAFFEINE-INDUCED NEUROTOXICITY

The American Academy of Pediatrics discourages the use of caffeine in children, including athletes, given the significant risk of adverse effects.[9] Potential risks with long-term caffeine overuse include disruption of sleep patterns, hypertension, physiologic dependence, and exacerbation of underlying psychiatric disease.[10] Children's brains are thought to be particularly susceptible to the effects of caffeine due to ongoing brain development.[11,12] Even with moderate dosing, adverse effects such as tremor, anxiety, insomnia, mood changes, gastrointestinal discomfort, decreased

attentiveness, restlessness, and psychosis can occur.[13] Caffeine has been shown to induce both de novo psychosis and mania and to exacerbate underlying psychiatric disorders. Therefore, patients being managed for psychiatric or behavioral conditions should be screened for caffeine use.[14]

CAFFEINE-INDUCED CARDIOTOXICITY

Cardiotoxicity has been reported with both accidental and intentional caffeine overdose, resulting in arrhythmia, ST segment elevation myocardial infarction, and cardiac arrest. Patients with underlying abnormalities such as channelopathies or concomitant drug or alcohol toxicity may be at particularly high risk for an adverse outcome.[15] One hypothesis for the mechanism of caffeine-induced cardiotoxicity is reduced myocardial blood flow.[16] 15 patients younger than 30 years old in the literature to have presented with energy drink–related cardiovascular toxicity, no underlying cardiac abnormalities were detected in the majority, indicating that such products can cause severe toxicity in patients who are otherwise healthy.[15]

Fatalities have occurred with ingestions estimated at 150 mg/kg[17-19] and with blood caffeine concentrations in the range of 80-100 mg/L, which could occur after the ingestion of 10 g of caffeine: about 50 caffeine pills (200 mg each) or approximately one tablespoon of anhydrous caffeine.[17,20,21] Added risk accompanies the overuse of caffeine through the ingestion of multiple concomitant stimulant products or products used in conjunction with physical activity.[8,15,22] Inadvertent overdose may occur when caffeine is dosed from multiple sources.

CASE REPORTS OF SEVERE CAFFEINE TOXICITY

There are a number of case reports of severe toxicity resulting from excessive caffeine ingestion. A 20-year-old woman presented with agitation, vomiting, tremor, and 23 episodes of pulseless ventricular tachycardia responsive to defibrillation after a suicidal ingestion of caffeine in powder and pill form.[23] Other reported toxicities have included seizures,[24-27] psychosis,[28] rhabdomyolysis with renal failure,[29] and hyperglycemia with acidosis and elevated lactate.[30] Severe overdose typically presents with hypokalemia; ventricular arrhythmias; early hypertension followed by hypotension; seizures; rhabdomyolysis; and, rarely, death from circulatory collapse.[31] Seizures are caused by adenosine antagonism in the central nervous system. Hypotension and tachycardia occur via β-adrenergic agonism. Metabolic derangements including elevated lactate and hypokalemia occur via stimulation of glycolysis and the sodium/potassium ATP-ase.[32] Severe overdoses are managed with supportive care, GABA agonists (benzodiazepines, barbiturates, propofol) for seizures, α-adrenergic pressors for refractory hypotension, and antiarrhythmics. For refractory ventricular arrhythmias, hemodialysis and intralipid have been used.[33]

ANHYDROUS CAFFEINE

Anhydrous (powdered) caffeine is sold as an additive for beverages and marketed as an energy supplement and stimulant product. Like other supplements, anhydrous caffeine is not regulated by the US Food and Drug Administration (FDA). However, after the 2014 anhydrous caffeine–induced fatalities of an 18-year-old male high school athlete and a 24-year-old recent college graduate, the FDA released a warning that powdered caffeine contains very high concentrations of the drug. One teaspoon of anhydrous caffeine contains the equivalent dose of caffeine found in "about 25 cups of coffee."[34,35] In 2015, the FDA sent warning letters to distributors of anhydrous caffeine regarding the narrow therapeutic to toxic ratios that preclude safe dosing for consumers. In this same statement, the FDA reported a plan to continue to "aggressively monitor the marketplace" and to take action as appropriate.[36]

Ingestion of an estimated 50 g of anhydrous caffeine resulted in ventricular fibrillation cardiac arrest requiring multiple rounds of defibrillation, antiarrhythmic agents, aggressive potassium and magnesium supplementation, and intensive care.[37] A retrospective case review of anhydrous caffeine ingestions reported to poison centers found that the majority of calls were due to inadvertent overdoses related to unclear package dosing instructions. Children aged 0-12 years had unintentional ingestions of beverages to which anhydrous caffeine had been added by an adult. Children more than 12 years of age typically had adverse reactions after the intentional self-administration of a beverage to which anhydrous caffeine had been added.[38]

A laboratory analysis of anhydrous caffeine products available on the Internet found that the products had a very high median purity (90%) and consistently lacked clear dosing instructions on packaging. This is concerning because a potentially lethal dose can be found in a single tablespoon of anhydrous caffeine.[39]

CAFFEINATED BEVERAGES

Caffeinated energy drinks represent a multibillion dollar industry that targets teens and young adults.[40] Sourced from natural products including coffee beans, tea leaves, cacao, kola nut, and guarana berries, caffeine is one of the most common ingredients consumed worldwide. The most common forms consumed are coffees, teas, and energy drinks.[7] The caffeine content in energy drinks ranges from about 80 to 500 mg compared with about 50 mg in an average 12-oz cola drink or 100 mg in a regular cup of brewed coffee.[41] Caffeinated energy drinks, which are reportedly consumed by 30-50% of adolescents and young adults, may contain unregulated ingredients and are products that are not required to quantify caffeine content.[42] This may place children and adolescents at risk, particularly those with a history of seizures, underlying cardiac abnormalities, or behavioral disorders already treated with stimulant medications.[28]

There are numerous reports of severe toxicity related to the consumption of caffeinated beverages, even among previously healthy individuals. A 28-year-old man experienced cardiac arrest after excessive consumption of a caffeine-containing energy drink.[43] A 17-year-old adolescent boy suffered ST-elevation myocardial infarction with reduced left ventricular systolic function following a large ingestion of caffeinated energy drinks.[44] A previously healthy 22-year-old woman experienced torsades de pointes with QTc of 526 milliseconds after drinking 6 cans of a caffeinated energy drink at a dance club.[45] According to pharmacokinetic modeling analyses of caffeinated energy drink consumption, peak serum caffeine concentrations after the ingestion of 1-2 energy drinks can overlap with those reported in caffeine-induced fatalities. This is of particular concern in younger consumers with lower body weights.[46]

A 2013 report from the Substance Abuse and Mental Health Services Administration's Drug Abuse Warning Network noted a doubling of emergency department visits for energy drink–related symptoms between 2007 and 2011. The majority of chief complaints were related to adverse reactions to the ingestion, with visits by males more than doubling those by females.[47] The demographic most affected by energy drink consumption is the adolescent and young adult male population. Most concerning are possible links to risky behavior including substance abuse.[1] Given ready availability and aggressive marketing, the use of energy drinks among adolescents and young athletes remains a significant and ongoing concern.[48,49] A survey of adolescent emergency department patients reported a mean consumption of 1.5 energy drinks per day on most days and "at most" a mean of 2.4 energy drinks per day.[50] Another survey of adolescents found that reasons for caffeinated energy drink use included the following: 61% to increase energy, 32% as a study aide, 29% to improve performance during sports, and 9% for weight loss. A concerning 24% reported combining energy drinks with ethanol or drugs (marijuana, methamphetamine, and cocaine), and 19% reported insomnia as an adverse effect.[51] A survey of 12- to 18-year-old patients found that frequent energy drink consumers were more likely to report headaches, anger, urinary frequency, and difficulty breathing and that these same patients believed that energy drinks improved athleticism (35%), improved wakefulness (67%), and improved concentration (34%).[52] A survey of high-school students found that users of energy drinks had a higher frequency of depression, "sensation seeking," and substance use.[53]

A national survey of youths with alcohol use found that the prevalence of caffeinated alcoholic beverages among underage drinkers was 52.4%, with a prevalence of 48.3% among age 13- to 15-year-olds and 45.3% among 16- to 18-year-olds.[54] An analysis of 1 year of United States National Poison Data System cases found that 50.7% of reported cases of ingestion of nonalcoholic caffeinated beverages were unintentional exposures in children younger than 6 years and that 68.2% of caffeinated alcoholic beverages were in patients less than 20 years old. A total of 76.7% of cases were referred to a health care facility, with rare severe cases resulting in toxicity that included seizure, dysrhythmia, and tachypnea.[55] The consumption of caffeinated alcoholic beverages is associated with binge drinking, prescription drug misuse, illicit drug use, increased frequency of intoxication, increased reports of being taken advantage of sexually as well as taking advantage of others sexually, being a passenger in a car with an intoxicated driver, physical altercations, becoming physically injured while intoxicated, and being found in "high risk public settings" such as a public park after dark.[10,54,56-59]

OVER-THE-COUNTER CAFFEINE ORAL MEDICATIONS

The removal of ephedra-containing dietary supplements from the US and Canadian markets in 2004 prompted increased availability of "ephedra-free" products. Many of these contain caffeine from multiple sources including synthetic and plant-based

sources.[22] Caffeine-containing supplements marketed as diet aids, performance enhancers, or energy boosters may cause toxicity, particularly with concomitant energy drink use.[22] Severe toxicity has been reported with large intentional self-harm ingestions of caffeine pills.[20]

OTHER CAFFEINE-CONTAINING PRODUCTS

Other caffeinated products on the market include water (Water Joe and Avitae), chewing gum (Stay Alert and Jolt), mints, candies (Snickers Charged), and peanut butter (STEEM).[60] Most concerning is the potential for the co-ingestion of caffeinated food products with other sources of caffeine such as energy drinks, caffeine pills, or anhydrous caffeine. With "stacked" doses from multiple sources of caffeine, inadvertent overdose risk is likely increased. There is potential for food-based caffeine products to be appealing to younger individuals, particularly products such as gums, candies, and sandwich spreads.

PATTERNS OF CONSUMPTION

The 2007-2010 National Health and Nutrition Examination Survey reported mean caffeine consumption of 25 mg/d for children age 2-11 years and 50 mg/d for children aged 12-17 years. Caffeine sources included sodas, teas, coffee, and flavored dairy beverages.[61] Among children older than 12 years, the highest consumption was among non-Hispanic whites with coffee as the most common source of caffeine. Younger children, aged less than 12 years, were more likely to consume sodas, teas, and flavored dairy drinks.[62]

REGULATION OF CAFFEINE-CONTAINING PRODUCTS

FDA regulation of caffeinated products varies dramatically. Caffeine content in cola beverages is not to exceed 0.02% to be classified as "generally recognized as safe."[63] Natural sources of caffeine such as kola nuts, guarana, and yerba mate do not have to be quantified and yet contribute to overall caffeine dose provided by a caffeinated product.[63] The 1994 Dietary Supplement and Education Act classifies products containing natural substances as "supplements," for which caffeine content is not mandatorily reported. Because noncola energy drinks often contain plant or herbal extracts, they are regulated as "supplements"; thus, the same maximum caffeine content limit placed on colas does not apply.[64] Product labels must indicate that the product "contains caffeine" for colas, energy drinks, foods with added caffeine, and over-the-counter drugs. Labels must specifically indicate the amount of caffeine in over-the-counter drugs, supplements to which dietary caffeine has been added, and colas but not in foods, noncola beverages, supplements with naturally occurring caffeine, foods with added caffeine, or energy drinks.[63,65,66] Over-the-counter stimulant medications containing 100 mg of caffeine must have a warning label about the adverse effects of excessive caffeine use. However, energy drinks (which often contain up to 5 times this amount of caffeine) are not required to use warning labels.[64]

In 2010, the FDA issued a warning letter to makers of alcoholic caffeinated beverages which resulted in the subsequent removal of several caffeinated alcoholic beverage products from the marketplace.[67] The concern was that the stimulant effect of caffeine would mask the intoxicating effects of the ethanol. This effect is sometimes called *wide awake drunk*, a state with potential to prolong the drinking episode and potentially increase concomitant "risk behavior."[68,69]

In 2013, the American Medical Association expressed concerns during a US Senate Committee hearing regarding the marketing of energy drinks to children.[70] The FDA continues to collect data and track consumption of caffeinated products.[63] In response to FDA pressure and public criticism, the Monster Energy™ company recently voluntarily added caffeine content information to their caffeinated energy drinks.[71] Although the FDA continues to examine the safety of caffeine ingestion in children and young adults, the responsibility to reduce or prevent harm in both the health care and consumer settings will likely fall on health care provider groups and policymakers.[72]

SUMMARY

The consumption of caffeine-containing energy drinks and supplements that are marketed to improve cognitive performance, wakefulness, or athletic prowess may not be commonly reported to health care providers. Health care providers should be aware of the potential toxicity of caffeine and should consider screening and counseling children and adolescents for caffeine use and risk factors for toxicity, particularly those being managed with a prescription stimulant for attention-deficit disorder.

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