The clinical toxicology of caffeine: A review and case study

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ABSTRACT

Caffeine is a widely recognized psychostimulant compound with a long history of consumption by humans. While it has received a significant amount of attention there is still much to be learned with respect to its toxicology in humans, especially in cases of overdose. A review of the history of consumption and the clinical toxicology of caffeine including clinical features, pharmacokinetics, toxicokinetics, a thorough examination of mechanism of action and management/treatment strategies are undertaken. While higher (i.e., several grams) quantities of caffeine are known to cause toxicity and potentially lethality, cases of mainly younger individuals who have experienced severe side effects and death despite consuming doses not otherwise known to cause such harm is troubling and deserves further study. An attempted case reconstruction is performed in an effort to shed light on this issue with a focus on the pharmacokinetics and pharmacodynamics of caffeine.

1. Introduction with a brief history of caffeine consumption

Caffeine (1,3,7-trimethylxanthine) is a psychostimulant purine-like alkaloid, which is found naturally in coffee, tea, cacao beans (source for chocolate and cocoa) guarana, mate, and kola nuts, though it has been identified in more than 60 plant species [1,2]. It has been consumed for thousands of years by humans with stories indicating the earliest consumption of boiled tea in China in the year 2737 BCE by the emperor Shen Nung, supposedly after tea leaves fell or blew into his boiling water [1]. Although this account may in fact be mythological, recent evidence demonstrates tea consumption in China as far back as 2,100 years ago during the Western Han Dynasty which ruled from 207 BCE to 9 BCE [3,4]. Prior to this recent discovery the first confirmed historical consumption of tea was 750 CE [3].

Coffee's introduction is similarly linked with mythology and ambiguity with legend indicating the first apparent consumption in either Ethiopia or the southern tip of the Arabian Peninsula in the 9th century by a shepherd who deduced that the wild coffee berries his goats consumed, were responsible for their display of increased energy. Consequently, the shepherd began consuming them and experienced what is now in modern times recognized as the central nervous system (CNS) stimulation from caffeine in the berries [1,5]. In reality the first use of coffee infusions with boiling water appears around 1000 CE [3]. However, caffeine would not be isolated as the active constituent of coffee's stimulating effects until 1819 followed by its first total synthesis in 1895 [6]. By the 14th century the roasting of coffee beans had been discovered and by the 15th and 16th centuries, knowledge of its

stimulating effect had apparently led to widespread consumption and commercialization in coffee houses in Arabia and Constantinople [3,7]. In the 17th century, once shipped from overseas the consumption of coffee in Europe became more common and consequently spread to the colonies in North America [1,3,5,7,8]. Tea and coffee have since served as the major beverage sources of caffeine but in the late 1800's caffeinated soda entered the marketplace in the branded products, Dr. Pepper, Coca-Cola and Pepsi-Cola becoming extremely popular during the second half of the 20th century [1]. Since then, the latest iteration of caffeinated beverages that have become popular are the so-called "energy drinks", which entered the market in the late 20th century and have since grown in popularity [9–11].

Nowadays, caffeine is the most widely consumed psychostimulant in the world. It is estimated, that caffeine is being consumed by more than 80% [1,12] of the world's and up to 89% of the United States population [10]. The average daily consumption of caffeine varies depending upon the survey, years conducted and sources considered but has most recently (i.e., 2011–2012) been reported as 142 mg per day for adults and children in the United States, a decrease from previous years (e.g., average consumption of 175 mg/day in 1999–2000) largely attributed to a reduction in soda consumption [11]. Coffee purchased from the grocery store and tea remain the largest contributors to caffeine intake in the United States overall, although the contribution from energy drinks, while still a relatively minor contributor overall has increased [10,11].

While caffeine is generally thought to be safe in moderate amounts (i.e., ≤ 400 mg per day) in healthy adults [13], it is clearly not an

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innocuous compound and can cause significant toxicity and even lethality (i.e., most commonly via myocardial infarction or arrhythmia) if sufficient quantities are consumed [13,14]. Some sensitive individuals may also experience toxicity and lethality at doses not normally associated with such outcomes [15,16].

The following review covers certain aspects of the clinical toxicology of caffeine including clinical features, pharmacokinetics, toxicokinetics, mechanism of action and management/treatment strategies. Finally, a case reconstruction of a 16 year old male whose death was attributed to acute caffeine toxicity in 2017 is performed [17]. This particular case has been viewed with some skepticism due to the seemingly low amount of caffeine consumed. A discussion of pharmacokinetics and pharmacodynamics of caffeine will be used to aid in a reconstruction of what may have occurred.

2. Clinical features

Caffeine is known to have generally dose-dependent effects with positive or desirable effects at lower doses (i.e., ≤ 400 mg) and undesirable effects generally above this level of intake, although there is substantial inter-individual variation [18,19]. For example, increased arousal, alertness, concentration and well-being (e.g., increased elation, peacefulness and pleasantness) have been noted at doses of 250 mg in human subjects [18,20], whereas a dose of 500 mg was shown to increase tension, nervousness, anxiety, excitement, irritability, nausea, paresthesia, tremor, perspiration, palpitations, restlessness and possibly dizziness [20]. High, sub-lethal doses (~7–10 mg/kg) in normal adults may also cause symptoms such as chills, flushing, nausea, headache, palpitations and tremor, although individual responses vary significantly [19–24].

As Turnbull et al. [19] have noted in a recent and extensive review of the literature to date, there is no "bright line" or acceptable daily intake which can be derived from such highly variable data as individual tolerance varies so greatly in this regard. Nonetheless, most governmental authorities have determined intake levels which are thought to be safe or lack any significant risk of serious adverse effects in healthy adults. The United States Food and Drug Administration (FDA), Health Canada and the European Food Safety Authority (EFSA) have all determined that a total daily intake of 400 mg of caffeine is unlikely pose a risk of serious harm to the general population of adults [25]. They do however, differ slightly in recommendations for children and adolescents with Health Canada recommending no more than 2.5 mg/kg and the EFSA recommending no more than 3 mg/kg per day [25]. For pregnant women, the daily intake of no more than 300 mg appears to be safe but no more than 200 mg may be prudent [25].

While intake levels below 400 mg per day are generally thought to be safe in healthy adults, individuals encountered in a clinical toxicology setting are likely to have ingested much larger, gram quantities [26–28]. In cases of overdose, often intentional but sometimes undetermined and unintentional, at least 5 g or more (i.e., often around 10 g but up to 50 g) have been ingested leading to fatalities particularly if the individuals are not treated in time or at all. However, doses up to 50 g have also been treated successfully otherwise [29,30]. Some have indicated that after a dose of around 1 g, toxic symptoms begin to manifest, a dose of 2 g requires hospitalization, while higher doses (e.g., typically 5 g or more) could be lethal [27,28,31]. However, some have determined that as little as 3 g could be lethal under certain circumstances [28,31,32]. One case describes rhabdomyolysis and acute renal failure in a male who ingested approximately 3.6 g of caffeine [32].

The clinical features of caffeine intoxication vary but have been reported to include cardiovascular symptoms (hypertension, hypotension, tachycardia, bradycardia, atrioventricular block, supraventricular tachycardia (SVT), ventricular tachycardia or ventricular fibrillation, myocardial ischemia, myocardial infarction, and cardiac arrest), gastrointestinal symptoms (nausea, vomiting, severe recurrent vomiting, abdominal pain, diarrhea), psychological/neurological symptoms (delusions, hallucinations anxiety, agitation, excitation, seizures,

headache, cerebral edema, coma), metabolic symptoms (hypokalemia, hyponatremia, hypocalcemia, metabolic acidosis, respiratory alkalosis, hyperglycemia, fever), musculoskeletal symptoms (weakness, rigidity, tremor, rhabdomyolysis), pulmonary symptoms (hyperventilation, respiratory failure), tinnitus, dizziness, diuresis, and death [21,26–29,33–35]. Renal failure and questionable hepatic injury (i.e., based only upon modest transaminase elevation which is known to occur in cases of rhabdomyolysis) secondary to rhabdomyolysis have also been reported [36,37].

2.1. Paradoxical effects

Some of the more paradoxical effects seen (e.g., hypertension-hypotension and tachycardia-bradycardia) may be explained by divergent molecular targets depending upon the concentrations experienced or more simply, divergent physiological responses to different exposure levels. For example, hypertension may be caused by increased catecholamine levels via presynaptic adenosine A1 receptor antagonism (and possibly blockade of the adenosine A1 receptor of the adrenal medulla) and inhibition of the vasodilatory effects of adenosine via adenosine A2 receptor antagonism, which can be experienced in cases where serum caffeine is in the therapeutic range [38–45]. Conversely hypotension may occur due to phosphodiesterase inhibition in cases of overdose/poisoning where much higher, toxic concentrations are reached (although, reduced cardiac output due to tachydysrhythmias is also likely: See *Mechanism of Action*) [38,46,47].

Similarly, bradycardia, when encountered may result from reflex bradycardia due to increased blood pressure from doses within the therapeutic range, while tachycardia is reported almost uniformly in cases of caffeine intoxication and high doses (e.g., > 10 mg/kg) of caffeine [21,38,46–51]. This is presumably due to the beta 1-adrenergic agonism via increased catecholamines, which ultimately results in increased levels of cyclic adenosine monophosphate (cAMP) via adenylyl cyclase activation and is said to be further enhanced by inhibition of the enzyme, phosphodiesterase which is responsible for cAMP's degradation [21,38,46–51]. However, adenosine (via agonism of the adenosine A1 receptor) exhibits an anti-adrenergic effect by inhibiting adenylyl cyclase activity thereby working to reduce intracellular cAMP accumulation and inhibiting subsequent downstream signaling [52]. Caffeine's antagonism of this receptor (adenosine A1) may further potentiate the downstream effects of beta 1-adrenergic agonism via increased catecholamines [38–44,52].

2.2. Potential mechanisms for serious cardiovascular side effects

With respect to arrhythmia in cases of caffeine intoxication, ventricular fibrillation is most often determined to be the cause of death [26], while the most frequently cited mechanisms for arrhythmia include increased catecholamine levels, phosphodiesterase inhibition, increased intracellular calcium and antagonism of anti-arrhythmic adenosine receptors (See *Mechanism of Action*) [47]. With respect to myocardial infarction, coronary artery vasospasm has been proposed as the cause [48]. Coronary vasospasm has been proposed to occur via caffeine's adenosine antagonism and catecholamine release which may increase vascular smooth muscle contraction causing vasoconstriction [53].

2.3. Differential diagnosis

While there are no definitive symptoms for diagnosis, vomiting or severe recurrent vomiting is often seen. The symptoms of hypokalemia and/or severe recurrent vomiting in individuals who have been known to have ingested psychoactive substances has in fact been recommended by some authors as a means of differential diagnosis for the determination of caffeine ingestion versus other sympathomimetic agents [34]. Certainly a patient presenting with symptoms of CNS stimulation (e.g., excitation, agitation, anxiety) and severe recurrent

vomiting with or without hypokalemia and reported psychoactive substance ingestion might be suspected of having acute caffeine intoxication [34].

2.4. Chronic effects

While the above discussion generally involves acute toxicity, chronic toxicity can also occur with caffeine. Some features can include hypokalemia, anorexia, nausea, vomiting, palpitations, seizures, dysrhythmia and a constellation of symptoms, referred to as "caffeinism", which is apparently indistinguishable from severe chronic anxiety and typically occurs with daily intakes of 1 to 1.5 g per day [18,38].

3. Pharmacokinetics

3.1. Absorption

Caffeine has rapid and complete (i.e., 99%) absorption from the small intestine after oral administration in humans due to its weakly basic nature and pKa of 14 at 25 °C, favoring an un-ionized/lipophilic state in the more basic environment of the small intestine where it may more easily partition into the lipid bilayer of cells, as compared to the acidic environment of the stomach where it is more ionized and less lipophilic [54–56]. When consumed with food and perhaps some beverages, absorption may be slower compared to ingestion of caffeine alone on an empty stomach presumably due to a delay in gastric emptying. Although, in the case of beverage-based studies evaluating absorption rates of caffeine, some have criticized such investigations for the failure to control for the volume of the prepared drink [38,54,57]. Nevertheless, the overall extent of absorption generally remains consistent.

Caffeine is not known to undergo significant first-pass metabolism and generally reaches peak plasma concentrations within 30–120 min after administration, although some individuals may fall outside of this range [54,57,58]. The ingestion of alcohol, nicotine and drugs along with age, gender and genetic variables do not seem to have a meaningful impact upon absorption as well [54]. While it has been speculated that the rate of consumption of a caffeinated beverage (i.e., drinking an "energy drink" or cold coffee rapidly versus slowly sipping hot coffee or an energy drink) may cause significant changes in the time to reach peak plasma concentrations, a study evaluating such variables did not find any statistically significant difference between the time to reach peak plasma concentrations [57].

The peak plasma concentrations demonstrate some variation but overall show fairly consistent values in healthy adults [20,54,58–64] (Table 1). What emerges as a central notion from these data is a moderate degree of variation in peak plasma concentrations after caffeine ingestion in humans. Indeed, Dorne et al. [65], reviewed and compiled pharmacokinetic data from several studies and found a mean coefficient of variation of 24.1% in healthy adults [65]. A proposed explanation for this variation is the inter-individual difference in

Table 1
Approximate Peak Plasma Concentrations (Cmax) after Oral Caffeine Administration in Healthy Humans.

Dose	Sex	Cmax	Note	Reference
5 mg/kg	Men	10 mg/L		[54,59]
5 mg/kg	Men	9 mg/L	Young and elderly men.	[60]
250 mg	Men & Women	7 mg/L		[20]
500 mg	Men & Women	17.3 mg/L		[20]
200 mg	Men	3.4 mg/L		[61]
400 mg	Men	7.4 mg/L		[61]
400 mg	Men	9.1 mg/L		[62]
2 mg/kg	Men & Women	3 mg/L		[63]
4 mg/kg	Men & Women	7.5 mg/L		[63]
100 mg	Men	2.5 mg/L	Administered as coffee.	[64]

Cytochrome P450 1A2 (CYP1A2) activity, which will be discussed in more detail elsewhere (See *Metabolism*).

3.2. Distribution

Caffeine is distributed throughout the body after being absorbed from the gastrointestinal tract (the small intestine in particular), entering all tissues via cell membranes (i.e., due to its lipophilic moiety or moieties and limited plasma protein binding) and entering intracellular tissue water [54,66,67]. It readily penetrates the blood-brain barrier as well [54,67]. As with all pharmacokinetic variables there is variation with the volume of distribution but an average of 0.7 L/kg is commonly noted [54,66]. It has rather low protein binding with around 10–35% reported [67]. Caffeine is also not known to accumulate in tissues [54,66]. Caffeine is often referred to as being lipophilic [60], but it is more accurately characterized as an amphiphilic molecule (i.e., logP = -0.07), which due to certain lipophilic moieties is able to partition into the lipid bilayer and diffuse across into the cell [68,69].

3.3. Metabolism

Caffeine is described by a single-compartment model where it follows first-order, linear kinetics [70], although some have noted that it may follow non-linear kinetics if the dose is high enough and its metabolism is saturated [20,54,65,70]. Caffeine is primarily metabolized to 1,7-dimethylxanthine (paraxanthine) in the liver via the CYP isozyme CYP1A2, which causes 3-demethylation of caffeine. Paraxanthine is the major metabolite (approximately 80%) of caffeine biotransformation [54]. Interestingly, paraxanthine itself is also pharmacologically active albeit with potentially lower toxicity than caffeine [71]. CYP1A2 is also responsible for, along with to some extent CYP2E1, the 1 and 7-demethylation of caffeine to 3,7-dimethylxanthine (theobromine) and 1,3-dimethylxanthine (theophylline), respectively, which are also pharmacologically active. Theobromine accounts for approximately 11%, while theophylline is around 5% of caffeine metabolites [54,66,67]. These metabolites may then be further demethylated via CYP1A2 primarily, acetylated via N-acetyltransferase 2, and oxidized via xanthine oxidase or CYP3A4 to yield the major metabolites which are excreted primarily in the urine including 1-methyluric acid, 5-acetylamino-6-formylamino-3-methyluracil, 1-methylxanthine (i.e., after further demethylation of paraxanthine via CYP1A2), 1,7-dimethyluric acid and 1,7-dimethylxanthine (paraxanthine) [54,66,67]. Overall, more than 25 metabolites have been identified in humans after caffeine administration, demonstrating rather complex metabolism [66]. It is important to note that the involvement of other CYP isozymes (e.g., CYP3A4/3A5 and CYP2D6) is only important at rather high (i.e., millimolar) concentrations rather than those normally encountered after typical caffeine ingestion [54]. Less than 5% of ingested caffeine is excreted unchanged [54,66,67].

There is significant inter-individual variation in CYP1A2 activity in humans, the majority of which is inherently due to genetics but to some extent environmental factors (e.g., smoking, *Brassica* vegetables, charcoal grilled meat and some medications such as omeprazole are all known to induce CYP1A2 activity while oral contraceptives, cimetidine, fluvoxamine and *Apiaceae* vegetables are known to inhibit CYP1A2 activity) which may mask genetic influences [54,58,66,72–77]. Coffee itself has been shown to increase CYP1A2 activity, although not consistently [54]. Other examples of inducers and inhibitors of CYP1A2 activity are given in Table 2 [78–92]. Demonstrating inter-individual variation, analyses at the population level have found coefficient of variation values of around 40% for CYP1A2 activity in humans [54,93].

3.4. Elimination

The vast majority of caffeine is eliminated from plasma via CYP1A2-mediated clearance in which paraxanthine is the main metabolite [94].

Table 2
Inducers and Inhibitors of CYP1A2 Activity in Humans.

Substance/Activity	Directional Change	Note	Reference
Fasting	↑	36 h fasted.	[78]
Fasting	↑	36 h fasted.	[79]
Grapefruit Juice	↔	200 mL single and repeat dose (1.2 L).	[80]
Grapefruit Juice	↓	300 mL repeat dose (1.2 L).	[81]
Ciprofloxacin	↓	750 mg x 3 doses. Effect is shared with many but not all quinolones.	[82,83,84]
Growth Hormone	↑	Healthy elderly men. Twelve week use.	[85]
Growth Hormone	↔	Growth hormone deficient children. Four week use. Similar results in six month study.	[86,87]
Herbal Dietary Supplement	↑	2-4 capsules x 3 days. Extracts containing kola nut, grape, green tea and *Ginkgo biloba*.	[88]
Heavy/Vigorous Exercise	↑	8-11 hours daily x 30 days.	[89,90]
Heavy/Vigorous Exercise	↑	Single maximal exercise cycle test in young hockey players.	[91]
Rifampin	↑	600 mg x 7 days.	[92]

Elimination occurs mainly via renal excretion in urine (~85–88%), although fecal excretion also takes place to a limited extent (i.e., around 2–5%) [24,54,95]. The clearance and elimination half-life of caffeine also show significant inter-individual variation. For example, the typical, average clearance value given is between 1 to 3 mL/kg/min, although a coefficient of variation of around 36% has been found [20,54,65]. Further complicating matters however; the clearance of caffeine can be substantially reduced as the dose of caffeine rises [20,54,65,70]. For example, while this is generally thought to occur at concentrations around 100 μmol (approximately 19.4 mg/L), there are data demonstrating it can occur with concentrations as low as 45 μmol (approximately 8.7 mg/L) [70], while others have indicated that this may occur at doses between 1–4 mg/kg [54]. This is thought to occur due to saturation of the CYP1A2 isozyme, likely by the main metabolite of caffeine, paraxanthine which is also a substrate for the isozyme [96].

However, others have noted there are conflicting data in this regard with some studies showing no decrease in clearance at doses normally consumed [97]. More recently this same group has noted the decrease in clearance with increased caffeine consumption but proposed that it does not involve saturation of the CYP1A2 isozyme [98]. This area deserves additional study. Since it has been estimated that the vast majority (> 95%) of caffeine's elimination from plasma is due to CYP1A2-mediated clearance [94], it is not surprising that those substances and activities which modify CYP1A2 activity also influence the clearance of caffeine. It is known that clearance can be reduced in pregnant women, those with liver disease, with grapefruit juice consumption, oral contraceptive use, and with alcohol consumption (See *Metabolism* and Table 2) [54,66]. Conversely, clearance can be increased by smoking and certain medications (e.g., rifampin, omeprazole and potentially growth hormone–See *Metabolism* and Table 2) [54,66].

Similarly and related to clearance, the elimination half-life is variable with an average of approximately 3–6 hours in healthy humans [54,66,67]. However, these values can vary substantially from 2.3 to 9.9 h once again demonstrating significant inter-individual variation [54]. Not surprisingly, those variables known to influence the clearance of caffeine have an effect upon the elimination half-life with those that decrease clearance generally prolonging the half-life and those that increase it decreasing the half-life [54].

4. Toxicokinetics

While it has been noted that the correlation between the serum concentrations of caffeine and clinical effects are poor, likely due to the substantial inter-individual differences in pharmacokinetics and pharmacodynamics, it is still of some general value [28,38,99]. In general, it has been noted that toxicological symptoms often begin above concentrations of 15 mg/L (i.e., generally more mild psychological side effects such as irritability and nervousness but also potentially palpitations, nausea, tremor, perspiration and paresthesia), while a concentration of 50 mg/L is considered "toxic" and concentrations of 80 mg/L or greater are considered lethal [20,21,26,27,31]. While a

minimum lethal concentration of 80 mg/L is rather well-supported to date [14–16,26,27,100], there is some evidence that there may be susceptible individuals who experience serious toxicity and lethality even below a concentration of 80 mg/L [14–16,27]. For example, some individuals with preexisting cardiovascular conditions appeared to have suffered lethality at a concentration below 50 mg/L [27]. Furthermore, in an analysis by Jones [14], out of 51 poisoning cases with caffeine-related fatalities the median serum caffeine concentration was 180 mg/L. However, the 10th and 90th percentiles were 84 and 314 mg/L, respectively. While the 10th percentile fits well with the minimum value established for lethality, the few cases that are below 80 mg/L and well below the 10th percentile (i.e., 5th percentile or lower) while clearly rare and potentially confounded by co-ingested drugs and pre-existing medical conditions, deserves attention and additional study.

5. Mechanism of action

The main proposed molecular target which caffeine is thought to interact with at physiologically relevant concentrations are the adenosine receptors [66,67,70,101,102]. These receptors of which there are at least four subtypes (i.e., A1, A2A, A2B, and A3) are G-protein coupled receptors or 7 transmembrane receptors [103], which activate G-proteins in the cell leading to various effects upon signaling molecules such as cAMP, arachidonate, choline, inositol triphosphate (IP3), and IP3/DAG (diacylglycerol) for example [104]. Specifically, caffeine has been shown to be a non-selective adenosine receptor antagonist with Ki values of 44 and 40 μmol (around 8.5 and 7.8 mg/L) for the adenosine A1 and A2A receptor subtypes, respectively, although others have reported even lower values [66,67,70,101,102]. However, the threshold for initial adenosine antagonism with caffeine is less than 10 μmol (1.94 mg/L), and potentially as low as 2 μmol (0.38 mg/L) [101,102]. The A1 subtype is mainly localized to the brain, spinal cord, eye, adrenal gland, heart and to a lesser extent, tissues such as skeletal muscle and adipose [70,104–106]. The A2A subtype is mainly localized to the spleen, thymus, striatopallidal GABAergic neurons and to a lesser extent the heart, lung and blood vessels [70,104–106]. Caffeine is also an antagonist at the A2B receptor subtype, though its tissue expression (i.e., mainly in the cecum, colon, bladder and bronchial smooth muscle) does not seem to be as toxicologically relevant as compared to the other receptor subtypes [70,104–106]. Regarding the A3 receptor subtype, caffeine does not have a high affinity for this and thus it is infrequently discussed [70].

While caffeine has often been referred to as a phosphodiesterase inhibitor, it is only able to interact with this molecular target at concentrations that greatly exceed those seen with normal caffeine consumption [39,66,67,70]. For example, the inhibition constant (Ki) value, which measures the affinity for phosphodiesterase by caffeine is 480 μmol (approximately 93.2 mg/L) while the half-maximal inhibitory concentration or IC50 value ranges from 500 μmol to 1000 μmol (approximately 97 to 194 mg/L, respectively) [66,67,70]. Thus, it is clear

that phosphodiesterase inhibition is unlikely to play any role in caffeine's mechanisms except perhaps in cases where very large, highly toxic and potentially lethal doses have been ingested.

Intracellular calcium release from skeletal muscle, cardiac muscle and neuronal tissue as a result of binding to and activating calcium-release channels (i.e., the ryanodine receptors or RyRs) has also been proposed [66,67,70,101,107–109] as a potential mechanism for caffeine's effects. Yet, it too requires concentrations that are unlikely to be achieved from normal caffeine consumption. For example, it has been noted that at least 250 μmol (approximately 48.5 mg/L) is required to cause any increase in calcium release while concentrations between 5 to 20 mM (approximately 971 mg/L to 3884 mg/L) are required for substantial increases in calcium release [66,67,101,107,108]. Thus, this is also unlikely to play a significant role in caffeine's mechanisms except perhaps in cases of large, toxic if not lethal overdoses. Similarly, caffeine has also shown activity as a potassium channel inhibitor but only at extremely high concentrations [110,111]. Other molecular targets such as the γ-aminobutyric acid receptor type A or GABA(A) have been proposed, but the Ki value for caffeine is 280 μmol (around 54.3 mg/L) and is once again unlikely to be achieved with normal or therapeutic consumption [101,102].

Aside from these mechanisms, caffeine is also known to increase catecholamine levels which can explain at least some of its physiological effects [66,67,96,112], and this effect may be due to antagonism at the presynaptic A1 adenosine receptor [38,40,44], and possibly antagonism of the A1 adenosine receptor in the adrenal medulla as well [43]. The antagonism of the A2A adenosine receptor is considered the most likely to explain caffeine's psychostimulant and dopaminergic effects [113].

Caffeine has also been proposed as having cholinergic effects as it has been shown to inhibit acetylcholinesterase with a Ki of 175 μmol (approximately 34 mg/L), a concentration that is once again only likely to be reached in cases of intoxication [114]. What becomes clear is that while caffeine has rather simple or less complex mechanisms in cases of normal use, in cases of toxicity and especially lethal doses, caffeine becomes a much more complex molecule potentially interacting with several molecular targets which may explain its side effects. For example, its antagonism of GABA(A) could explain the reports of seizures, although others have also pointed out the role of adenosine antagonism as well, with A1 agonism producing anticonvulsant activity and A1 antagonism lowering seizure threshold by increasing the release and activity of excitatory amino acids/neurotransmitters [38,115,116].

5.1. Mechanisms for specific side effects

5.1.1. Hypertension-hypotension

While hypertension is typically noted to be due to increased catecholamine release via adenosine antagonism (as well as direct vasoconstrictive response due to adenosine antagonism itself) after intake of therapeutic amounts, it is interesting that hypotension is frequently noted in cases of severe overdose and perhaps phosphodiesterase inhibition plays a role [38–42,47,117,118]. It should also be noted that the hypertensive effects of caffeine diminish with chronic consumption [119–121]. Hypotension has typically been attributed to two mechanisms, tachydysrhythmias due to caffeine causing reduced cardiac filling and subsequently decreased cardiac output, and increased catecholamine levels agonizing beta 2-adrenergic receptors, along with phosphodiesterase inhibition, resulting in vasodilation [46,47,122,123].

5.1.2. Questionable role of beta 2-adrenergic agonism in hypotension

The role of catecholamines and beta 2-adrenergic agonism in causing hypotension seems questionable. Specifically, such a mechanism implies that catecholamine release is responsible for both hypertension and hypotension despite the fact that beta 2-adrenergic agonism would occur in both instances. Conditions such as pheochromocytomas, which have even drawn comparative references to caffeine

intoxication can result in substantial increases in catecholamine levels, yet rather than hypotension are characterized by hypertension [122,124,125]. Furthermore, selective beta 1-adrenergic blockers such as esmolol and metoprolol would not be expected to yield beneficial effects upon hypotension in cases of caffeine intoxication if it is due to beta 2-adrenergic agonism, yet they have demonstrated benefit [48,126]. If however, the reduced cardiac output due to tachydysrhythmias is the cause of hypotension, reversal by a beta 1-adrenergic antagonist would be an expected outcome [126]. Thus, it seems that reduced cardiac filling and output and potentially phosphodiesterase inhibition are more likely to be the cause of hypotension.

Some have argued that beta 2-adrenergic agonism (via increased norepinephrine and epinephrine especially, along with phosphodiesterase inhibition) is a mechanism for caffeine-induced hypotension based upon the use of the methylxanthine, theophylline in the treatment of asthma and chronic obstructive pulmonary disease (COPD) and its side effects which share commonalities with those of beta 2-adrenergic agonists [127]. However, as more data have become available theophylline's therapeutic effects in asthma and COPD are now thought to be due to several potential mechanisms including phosphodiesterase inhibition (to a lesser extent), antagonism of adenosine receptors (especially A2B) and potential anti-inflammatory effects via inhibition of phosphoinositide 3-kinase-δ (PI3K-δ) and increased histone deacetylase (HDAC) activity [128,129]. The notion that theophylline's therapeutic or toxic effects are due to beta-adrenergic agonism however, is not well-supported [128,130].

5.1.3. Hypokalemia

The hypokalemia often noted in cases of overdose is likely due to activation of the Na+/K+ pump or Na+/K+ -ATPase [70]. While caffeine-induced hypokalemia is often claimed to be due to beta 2-adrenergic agonism stemming from catecholamine release, a role due to either adenosine antagonism or phosphodiesterase inhibition (i.e., in cases of overdose) is also possible [38,122,123,131–133]. For example, even rather low or moderate doses of caffeine which have not caused substantial increases in plasma catecholamine levels have still been shown to decrease serum potassium [134–137]. Thus, a direct role for adenosine antagonism seems more likely with therapeutic use, while increased epinephrine from higher doses may further play a contributory role.

5.1.4. Difficulties in identifying mechanisms for specific side effects

The wide range of potential effects upon catecholamines, calcium-release channels, potassium ion channels, ATPase ion pumps, GABA(A) receptors, phosphodiesterase and acetylcholine presents difficulties for determining individual roles for some adverse effects in cases of severe intoxication. Of course, perhaps an obvious question is also whether adenosine antagonism itself is responsible for at least some of the toxicological effects seen with caffeine after significant ingestions. While some have suggested with at least some evidence that caffeine's effects at high doses are not due to adenosine antagonism [138], it is interesting to note that the adenosine A1 receptor antagonist, rolofylline was associated with an increased risk of seizure and stroke in clinical trials. These side effects and lack of efficacy led to its abandonment [116]. Others have indicated that adenosine antagonism could potentially cause cardiotoxic effects as well and adenosine itself is an anti-dysrhythmic [38,47,139]. Clearly this is also an area which deserves additional study.

6. Management/treatment strategies

Caffeine intoxication is essentially treated with supportive care, although there are techniques for decontamination and increased elimination which have been shown to be effective [29,38]. The approach for management or treatment depends upon the particular patient's symptoms, physical condition and the circumstances of their

ingestion. For example, a mild overdose of 1 g with an individual displaying only mild side effects (e.g., restlessness, irritability, palpitations) might simply be monitored and perhaps administered a benzodiazepine whereas someone with a massive overdose might require numerous interventions [30,38]. Hemodialysis has also been effectively employed to reduce caffeine in plasma while decreasing morbidity in cases of intoxication [38,46,47,140,141].

6.1. Cardiovascular side effects

Hypotension should first be treated with isotonic intravenous fluid but if needed, it can be treated with vasopressors such as phenylephrine (or epinephrine alternatively) while beta-adrenergic antagonists such as esmolol or propanolol have also been used in rarer cases of refractory hypotension [38,48]. The use of a beta-adrenergic antagonist in an already hypotensive patient may seem contradictory or illogical but has been proposed to be effective by inhibiting beta 2-adrenergic-mediated vasodilation and reversing beta 1-adrenergic-induced tachycardia and the associated decrease in cardiac filling and output [38,46,47,122,123].

Supraventricular tachycardia (SVT) due to caffeine intoxication is ideally treated with a benzodiazepine which is believed to reduce catecholamine levels through CNS inhibition and potentially increasing adenosine levels by inhibiting its reuptake [38,48]. While speculative, benzodiazepines may interact with the tryptophan-rich sensory protein, otherwise known as translocator protein (18 kDa) or TSPO, formerly known as the peripheral benzodiazepine receptor (PBR) and this may potentially have more direct pharmacological effects which may allow for cardioprotection, although there is still a great deal of work which remains to fully elucidate the role of this protein and its relationship with benzodiazepines [38,142–144]. SVT due to caffeine intoxication can also be treated with calcium-channel blockers such as diltiazem or verapamil [38,48]. Ventricular dysrhythmia can be treated with anti-dysrhythmics such as amiodarone, lidocaine or procainamide while beta-adrenergic antagonists such as esmolol have also been used either alone or in combination with anti-dysrhythmics along with electrolyte correction as needed [29,38,48,126,145].

6.1.1. The unopposed alpha effect

While the hypothesis of the "unopposed alpha effect" has risen as a concern with selective beta-adrenergic antagonists (e.g., esmolol) used for treatment in cases of sympathomimetic intoxication, it does not seem to be a concern in the case of caffeine overdose, with proponents of the hypothesis noting that unlike other sympathomimetic agents, caffeine intoxication typically presents with ventricular tachycardia and hypotension as opposed to the hypertension and tachycardia seen with stimulants such as cocaine [127,146].

Furthermore, several groups have recently begun to question the entire hypothesis of the unopposed alpha effect, noting that it has been incorrectly applied to any sympathomimetic agent, despite limited evidence of its utility in cocaine-based intoxications where its occurrence is inconsistent, rare and unpredictable [146–149]. Others have indicated that the unopposed alpha effect may in fact be more myth than reality, noting the original hypothesis may have simply been a misinterpretation of a phenomenon seen with Starling's law while noting the lack of consideration for factors other than vascular tone which control blood pressure [150]. Starling's law indicates that a decrease in heart rate as a result of beta 1-adrenergic antagonism could increase end diastolic pressure and cardiac fiber length, causing an increase in ventricular contraction and blood pressure [149,150]. Authors have also pointed out the lack of the unopposed alpha effect phenomenon despite widespread use of beta adrenergic antagonists to treat various sympathomimetic intoxications, including cocaine [146–150]. Some have indicated that the unopposed alpha effect may simply be a result of the pharmacological effects seen with cocaine intoxication, while others have indicated that the potential unopposed

alpha effect seen after propranolol administration in cocaine intoxication may not be a class effect but is unique to propranolol itself [148,149]. At the very least, for non-cocaine based intoxications involving sympathomimetic agents such as caffeine, it appears that this phenomenon should not cause clinicians to avoid treatment with a beta-adrenergic antagonist [127,146]. For other sympathomimetic agents, after a thorough and critical assessment of a given patient and symptoms, the use of a non-selective alpha and beta-adrenergic antagonist such as labetalol has been proposed [148,149]. It is also interesting to note the successful treatment of combined sympathomimetic intoxications with labetalol [151,152].

6.1.2. No standardized method of treatment
Some rather massive overdoses have been successfully treated with isotonic sodium chloride solution, sodium bicarbonate and hemodialysis [36]. However, there is no standard method for treatment of caffeine overdose or toxicity [153]. In the case of hypotension however, isotonic intravenous fluid should be a typical first approach followed by additional interventions if necessary [38,48].

6.2. Gastrointestinal side effects

The gastrointestinal side effects with caffeine are generally related to recurrent vomiting [34,38]. For this anti-emetics such as metoclopramide or ondansetron are recommended [38]. Cimetidine should be avoided as it may reduce the clearance of caffeine [38,58,75].

6.3. Psychological side effects and seizures

For side effects such as agitation, anxiety and seizures, benzodiazepines are recommended although barbiturates and propofol could also be used as a second-line therapy for seizures that are refractory to benzodiazepines [38,48]. Benzodiazepines are thought to be useful not only due to their effects upon GABA(A) receptor activity but also their ability to inhibit the reuptake of adenosine, making them potentially useful particularly in cases of caffeine-induced seizure [38]. Of course, this same mechanism may cause caffeine-induced seizures to be refractory to benzodiazepines in cases of severe intoxication.

6.4. Metabolic side effects and rhabdomyolysis

In cases of metabolic acidosis and hypokalemia, sodium bicarbonate and potassium chloride have been used, respectively [36–38]. In the case of rhabdomyolysis, intravenous fluid resuscitation is most important but sodium bicarbonate might also be helpful [32,36–38].

6.5. Decontamination and enhanced elimination

Regarding decontamination, activated charcoal is preferred and is considered by some as "essential" as caffeine adsorbs well to the activated charcoal and is often employed if the patient presents within a reasonable time frame (i.e., 1–2 h) [30,38,48,145]. Whole bowel irrigation could hypothetically be employed in a case where extremely large amounts of sustained release caffeine have been ingested. This seems less likely to be necessary, yet there are indeed sustained release caffeine formulations available on the market [154].

With respect to enhanced elimination the use of intralipid has apparently shown some success while hemodialysis alone or in combination with intralipid also seems successful [29,30,38,153,155]. The "intralipid" is a lipid emulsion that is administered intravenously and by acting as a "lipid sink" is able to remove caffeine (which displays some lipophilicity as an amphiphilic molecule) from tissues such as the brain and heart. Although, it should be noted that some have taken issue with the use of the term, "sink" to describe the effects of intralipid, instead stating that its actions more accurately reflect a "shuttle" or a "scavenger" that moves drugs from more to less perfused organs [30].

These same authors have also pointed out that intralipid may cause unintended consequences by interfering with other medications which are administered as a result of caffeine intoxication such as esmolol and especially amiodarone (i.e., more lipophilic compounds which may themselves be "shuttled"), causing them to lose efficacy in the desired organs. Hemodialysis on the other hand is effective at removing caffeine due to caffeine's low volume of distribution (0.7 L/kg) and low plasma protein binding (10–35%), which makes it amenable to this technique. It has been used either alone or in combination with hemoperfusion and has proven successful [38,46,47,140,141]. Hemoperfusion alone while not performed as often due to practical limitations has also been used in the past [38,156].

7. A case reconstruction

In May of 2017, reports of a 16 year old male in South Carolina, who had apparently died after ingesting caffeine-containing beverages in close succession, received national attention [17,157–160]. This particular case seemed to garner attention because the amount of caffeine was not considered lethal and the teenager was apparently otherwise healthy and had no reported medical conditions or allergies. The following is a case reconstruction with discussion of what may have led to this outcome.

During the school day a 16 year old male had ingested within a 40 min period, three caffeine-containing beverages, collapsed and was pronounced dead at the hospital after transport [17,157–160]. The coroner's cause of death was determined as, "due to a caffeine-induced cardiac event causing a probable arrhythmia." The coroner indicated that he believed the death was due to the ingestion of the three beverages over a short period of time [159]. The coroner also indicated that the young male was otherwise healthy and had no signs of any cardiac abnormalities at autopsy. It is unknown what, if any symptoms the young male experienced before collapsing. Due to privacy laws in the United States only limited information is publicly available. The beverages ingested were said to be a large diet Mountain Dew, a cafe latte from McDonald's and an unknown energy drink that was "chugged" or consumed rapidly, all at once. The male's weight was listed as being approximately 91 kg and his height was apparently around 1.73 m yielding an approximate body mass index (BMI) of 30.4 [161].

7.1. Dose ingested

While the exact dose of caffeine ingested by the young male is unknown, an estimate may be obtained based upon the drinks that were reportedly ingested. For example, the amount of caffeine in a "large", presumably 591 mL serving of diet Mountain Dew is approximately 92 mg [162]. The size of the café latte is not given in media reports but McDonald's is known to serve 355, 473, and 591 mL sizes [163]. Furthermore, there are no firm figures for the caffeine content of a McDonald's café latte or any latte. For example, a Starbucks café latte is said to have approximately 75 and 150 mg for a 355 and 473 mL serving, respectively [164,165]. A 591 mL serving would presumably have 225 mg. To further confound matters, some have reported concentrations of 121 mg caffeine in only 237 mL while others have reported similar values of around 109 mg per 237 mL serving, approximately 163 mg in a 355 mL serving and 272 mg in a 591 mL serving. Others have reported a range between 0.31 and 0.46 mg per mL (e.g. 183 to 272 mg for a 591 mL latte) [166,167]. Although, this variation is not surprising considering coffee is a natural product and thus is prone to variation not only from the raw product but how it is processed, extracted and prepared for consumption [166]. In any event, such data may at least give a range. Finally, the young male was reported as having consumed an energy drink all at once, the name or brand of which is not available. Once again, the caffeine content of these beverages can vary widely with some containing up to 357 mg in a single

473 mL can [165]. Most on average however, seem to contain approximately 160 mg [165], and this may represent the most likely consumption. Thus, this yields a total ingested amount of between 327 mg (assuming consumption of a 591 mL diet Mountain Dew containing 92 mg of caffeine, a 355 mL café latte containing 75 mg of caffeine and an energy drink containing 160 mg of caffeine) and 524 mg (assuming consumption of a 591 mL diet Mountain Dew containing 92 mg of caffeine, a 591 mL café latte containing 272 mg of caffeine and an energy drink containing 160 mg).

7.2. Estimated pharmacokinetics

The young male had an apparent bodyweight of approximately 91 kg, thus the dose consumed could have been between 3.60 and 5.75 mg/kg. This is well below the total dose (i.e., often a total dose of 5 g or more) or dose by bodyweight (i.e., often estimated at between 150–200 mg/kg) which is known to be lethal [33]. While a serum caffeine level of the young male has not been reported one might estimate via two methods, although it should be noted that both are highly speculative.

One method involves a simple calculation derived from Jones [14], who albeit controversially, uses a variation of this formula to determine the potential dose of caffeine ingested based upon known post-mortem concentrations in a deceased individual by taking the post-mortem concentration multiplied by the known volume of distribution and the bodyweight of the decedent [14,38]. In this case, conversely, the post-mortem concentration of caffeine in serum is unavailable but there is an estimated level of caffeine intake prior to death. Thus, one will instead take the known volume of distribution of caffeine (average of 0.7 L/kg) and multiply by the known bodyweight of the decedent (approximately 91 kg) and divide by the suspected dose (i.e., 327 to 524 mg) to yield what (i.e., hypothetically, the concentration found if caffeine is distributed into all body fluids completely and equally) the possible concentration at the time of death in mg/L [14]. This also assumes that caffeine is completely and equally distributed into total body water which others have indicated is indeed the case [168]. This concentration is also at zero time and thus does not account for any elimination. Thus [(*327 to 524 mg* / (*0.7 L/kg* x *91 kg*)], results in estimated values between 5.13 mg/L and 8.23 mg/L. While these figures are again speculative, if accurate these concentrations are not normally known to be toxic let alone lethal in healthy individuals.

Another method of estimating the possible plasma concentrations is based upon data from others. For example, a Monte Carlo simulation in adolescents up to the age of 15, determined that males with a bodyweight of 84 kg ingesting a dose of 320 to 484 mg may have a range of peak plasma concentrations between 1.8–10.2 mg/L and 2.7–15.5 mg/L, respectively [15]. However, these concentrations are not in the range normally associated with serious toxicity and lethality.

7.2.1. Potential role for CYP1A2 polymorphism

While myocardial infarction and the arrhythmia determined as a cause of death for the 16 year old male are distinct conditions, there is evidence to suggest a potential for overlap in some respects. For example, if coronary vasospasm occurs it may lead to myocardial infarction but it may also potentially lead to cardiac arrhythmia and sudden death and thus myocardial infarction may serve as a potential surrogate for risk of arrhythmia due to coronary vasospasm [53,169]. With this in mind, there are CYP1A2 polymorphisms which can result in some individuals metabolizing or clearing caffeine at a much slower rate (it should be noted however, that being a "slow" metabolizer does not mean a higher peak plasma concentration is reached after a given dose but may result in higher area under the curve (AUC) concentrations due to decreased clearance), increasing their risk of myocardial infarction and stroke from caffeine intake [170–173]. For example, in a case-control study evaluating the relationship between the risk for nonfatal myocardial infarction and coffee intake it was shown that the

adjusted odds ratios and 95% confidence intervals for those who possessed the "slow" CYP1A2 genotype were 1 (reference value), 0.99 OR, CI [0.69–1.44]; 1.36 OR, CI [1.01–1.83]; and 1.64 OR, CI [1.14–2.34] for those consuming < 250 mL, 250 mL, 500–750 mL and ≥ 1000 mL of coffee per day, respectively [171] which would presumably contain around 100 mg of caffeine per 250 mL [164,165,167]. For those with the "fast" genotype the odds ratios were 1 (reference), 0.75 OR, CI [0.51–1.12]; 0.78 OR, CI [0.56–1.09]; and 0.99 OR, CI [0.66–1.48], respectively. Interestingly, for those individuals that were younger than age 59 the odds ratios for the "slow" genotype were 1 (reference), 1.24 OR, CI [0.71–2.18]; 1.67 OR, CI [1.08–2.60]; and 2.33 OR, CI [1.39–3.89] for those consuming < 250 mL, 250 mL, 500–750 mL and ≥ 1000 mL of coffee per day, respectively. After statistical analyses the authors found there was a significant gene-coffee interaction only amongst the younger participants in the study. The authors also note that other groups have previously suggested that coffee is associated with an increased risk of myocardial infarction among younger individuals [171]. Consequently, the authors analyzed those with the "slow" genotype, under the age of 50 and determined odds ratios and 95% confidence intervals of 1 (reference), 2.12 OR, CI [0.86–5.24]; 2.43 OR, CI [1.22–4.82]; and 4.07 OR, CI [1.89–8.74] for those consuming < 250 mL, 250 mL, 500–750 mL and ≥ 1000 mL of coffee per day, respectively. For those with the "fast" genotype the odds ratios and 95% confidence intervals were 1 (reference), 0.39 OR, CI [0.15-0.97]; 0.35 OR, CI [0.17-0.76]; and 0.81 OR, CI [0.32–2.05], respectively.

Similar relationships with respect to CYP1A2 genotype and an increased and decreased risk for hypertension in slow and fast metabolizers respectively have also been shown [174]. The data clearly indicated that individuals with a "slow" genotype who consumed higher amounts of coffee had an increased risk of non-fatal myocardial infarction, while those with a "fast" genotype not only had no increased risk but a seemingly decreased risk [171]. It is also interesting to note that the risk increased as the dose of coffee increased. Perhaps most interesting is that those with the "slow" genotype and a younger age had the highest risk of non-fatal myocardial infarction (i.e., approximately 4-fold) relative to controls.

It is tempting to speculate that the 16 year old male in this case reconstruction, due to his young age and a possible "slow" genotype could have resulted in death possibly due to coronary vasospasm and subsequent arrhythmia [53,169,171]. However, it seems unlikely that this would fully account for this particular death. First, if indeed young age and a "slow" genotype were all that were required for such an event to occur the number of reported cases such as this would be expected to be much higher and would not be considered "rare" as in this case. The "slow" caffeine metabolizing genotype for example is present in some populations at greater than 50%. The Swedes for example, appear to have around 56% of their population with a "slow" genotype [175]. Sweden also has one of the highest rates of coffee consumption in the world [176]. Thus, if this were the only factor necessary for such an event, many more cases would be expected in younger individuals.

One potential explanation for this discrepancy could be that those with a CYP1A2 polymorphism resulting in "slow" metabolism are less likely to consume higher amounts of coffee or caffeine, perhaps due to negative experiences after consumption leading to behavioral changes. However, observational and interventional data have failed to find an association between CYP1A2 polymorphism and coffee and caffeine intake [177,178]. Additionally, there is a rather large body of evidence demonstrating an overall lack of risk for sudden death, arrhythmia and myocardial infarction in the population as a whole even with rather high intakes of caffeine [119]. This however, does not rule out a partial role if indeed this individual possessed a polymorphism for the CYP1A2 gene associated with slower caffeine clearance and a higher risk of myocardial infarction. Although, recent data indicate that in smaller samples of individuals, CYP1A2 genetic polymorphisms account for only a modest effect upon AUC concentrations when environmental factors (e.g., smoking and hormonal contraceptives) are excluded. Such

environmental factors may substantially mask the role of genetics [73].

One other consideration is that perhaps a 16 year old might metabolize caffeine at a different rate than adults. However, data indicate that by the time an individual reaches the age of 16 years, the pharmacokinetic profile of caffeine is similar to that of adults [179–183]. CYP1A2 activity is negligible in the fetus and slowly increases after birth, reaching approximately 50% of adult values by the first year [184]. Sometime after 1 year of age with some data indicating by the age of 3 years, CYP1A2 activity reaches levels comparable to those seen in adults [184,185]. However, between the ages of 3 to 9 years there is evidence for increased CYP1A2 activity up to 50% greater than adults, which still remains 33% greater from 9 to 15 years [184]. Upon reaching puberty (i.e., Tanner stage II for females and Tanner stages IV/V for males) CYP1A2 activity declines to reach adult levels [181,185,186]. Some have found that adolescents (i.e., 10–15 years of age) appear to be more sensitive to the effects of caffeine than adults but this appears to be related more to a lower relative bodyweight [15].

7.2.2. Role of rapid caffeine consumption

While some individuals such as the coroner in this case have speculated that the rapid consumption of caffeine was a factor a recent study has found this unlikely to be the case [57]. However, the consumption of caffeine over a small timeframe such as 40 min versus over an entire day will obviously lead to higher peak plasma concentrations but the single-dose consumed by the young male is consistent with doses that have also been studied as single-administrations and thus plasma concentrations reported in the literature are likely similar to what he experienced.

7.3. Potential pharmacodynamic explanations

While a pharmacokinetic explanation alone does not appear sufficient to explain this particular case there are also other considerations. For example, there are data demonstrating that some individuals possess a polymorphism associated with decreased catechol-o-methyltransferase (COMT) activity and that this decrease is associated with an increased risk of acute coronary events linked with coffee intake [119]. This is important to consider in the context of caffeine as it is known to increase catecholamine levels as one potential mechanism. It is conceivable that individuals with a mutation for this gene could have lowered COMT activity and thus might be more susceptible to the increase in norepinephrine/epinephrine and its effects upon cardiac function. There are also known mutations for the adenosine receptor gene (specifically the A2A receptor) which may also cause an increased sensitivity by some. Although, it is important to note that such mutations have only been linked to differences in sensitivity to the psychological effects of caffeine rather than cardiovascular [19,119]. However, mutations in the adenosine receptor have been linked to infarct size in patients with ischemic cardiomyopathy indicating a possible role in the response of the heart to ischemia or injury [187]. Adenosine may play a protective role in response to stress, inflammation and injury to cardiac tissues and it is a known anti-dysrhythmic [38], thus it is at least conceivable that mutations in these receptors may exacerbate any potential negative effects of caffeine upon these receptors and/or the prevention of their beneficial or protective effects by antagonizing them [188,189]. This is an area worth further exploration.

7.3.1. Other potential mechanisms of toxicological relevance

Aside from those discussed previously, other mechanisms could be involved. For example, caffeine has been shown to act as an inhibitor of the Human Ether-a-go-go (hERG) potassium channel which is found in different tissues including the heart [110,111]. The blockage of this channel has been implicated in the cause of cardiac arrhythmia in certain circumstances by causing QT prolongation [111]. However, as with many other molecular targets, hERG requires rather high concentrations for significant interaction with caffeine. For example, the

IC50 is around 5 mM (around 971 mg/L), making it highly unlikely to play a role in this particular death. However, authors have pointed out that around a 5–10% inhibition of this channel could be achieved with a concentration of 300 μmol (around 58 mg/L) [111]. Furthermore, caffeine may begin to have a small effect upon intracellular calcium release at these concentrations (i.e., at 250 μmol or approximately 48.5 mg/L) while *in vitro* data have shown potential pro-arrhythmic action attributed to an effect upon the cardiac ryanodine receptor (RyR2) cytosolic calcium sensitivity and increased RyR2 opening frequency [66,67,101,107].

Additionally, as some authors have found, the inhibition of hERG can be dramatically increased when two compounds with inhibitory effects are combined [111]. Thus, it is also possible that one of the constituents in the energy drink may have such activity and also contributed to the death by lowering the threshold for inhibition. Indeed, a recent study in healthy individuals found that compared to an equivalent amount of caffeine ingested alone, an energy drink demonstrated QTc prolongation at 2 h post-administration [190]. While this study had several limitations (e.g., the comparison was only significant relative to the caffeine group which demonstrated a decrease in QTc interval and the prolongation was transient, lacked placebo, food intake was not controlled for and ECG parameters were machine-calculated rather than measured by hand) it provided the first direct evidence that the combination of ingredients in at least some of these drinks may have divergent physiological effects upon cardiovascular variables compared to caffeine alone [190]. However, further study addressing the limitations of this study is needed to confirm these findings.

7.3.2. Potential clues from previous cases

An examination of other cases may offer clues in the case of the young male. For example, a 17 year old male experienced transient coronary artery vasospasm after ingesting 3–4 cans of Red Bull containing 80 mg each and 2–3 Monster energy drinks containing 160 mg each (total caffeine intake between 560–800 mg) before he arrived at an emergency room complaining of chest pain [53]. Another case involved a healthy 19 year old male who experienced cardiac arrest after consuming 3 cans (approximately 240 mL each) of Monster energy drinks over a 2 h period [191]. Several other case reports have been published concerning caffeinated energy drinks where the patient similarly consumed several drinks and ultimately experienced either myocardial infarction (i.e., ST-Elevation Myocardial Infarction or STEMI) or arrhythmia [191–193]. In another case a 44 year old woman developed nausea, vomiting, chest tightness, muscle twitching, palpitations and rhabdomyolysis six hours after ingesting approximately 1000 mL of coffee (estimated caffeine intake was 565 mg or 14 mg/kg body weight) [37]. In this particular case however, toxicity may have been related to her lower bodyweight (i.e., around 40 kg), allowing for high plasma concentrations to be reached. Lower bodyweight has been indicated as a potential cause for caffeine toxicity in some [15] however, this is not particularly relevant in the case of the 16 year old male in South Carolina as his bodyweight was not low.

There is also the possibility that this young male's ingestion of a large amount of caffeine unmasked congenital long QT syndrome as this has been previously reported in several cases [191,194]. Considering that a majority of deceased individuals with long QT syndrome (i.e., long QT syndrome is associated with sudden cardiac death) who died before the age of 50 were 20 years of age or younger along with a mean age at diagnosis of 21 years [195], this may represent a potential opportunity to reduce the risk of some fatal events by limiting access to certain energy drinks prior to adulthood. Another potential explanation is a genetic mutation of the RyR2 gene (which is also associated with sudden cardiac death) resulting in a greater sensitivity to the arrhythmogenic potential of caffeine [196,197].

7.3.3. Potential connection to sudden cardiac death

Sudden cardiac death (SCD) is a sudden and unexpected death resulting from rapidly occurring cardiac arrest outside the reach of a hospital or emergency room [198]. Incidence rates vary according to definitions, data sources and methods, demonstrating a range of 52.5 per 100,000 person-years in Asia to 111.9 per 100,000 person-years in Australia [198]. Seemingly corroborating such data, in prospective studies using standardized definitions in the United States, Netherlands, Ireland and China, SCD had an incidence rate of 40–100 per 100,000 person-years with China displaying the lowest rate [197]. SCD is much rarer in young adults and children under the age of 35 accounting for less than 1% of cases [198]. Some of the potential causes include coronary heart disease (CHD) which accounts for the majority of cases in those over the age of 35, while valvular heart disease, cardiomyopathies, myocarditis, and primary arrhythmia syndromes account for most of the remainder [198,199]. In individuals between the ages of 1 to 35 years, cardiomyopathies (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), myocarditis and primary arrhythmia syndromes (e.g., long QT syndrome-LQT, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia-CPVT, early repolarization syndrome) are the most frequent causes. In many cases, causes are inherited or have an underlying genetic basis [198,199].

Interestingly, the results of a population-based, prospective study conducted in New Zealand and Australia from 2010 through 2012 found the annual incidence of SCD amongst children and young adults aged 1 to 35 to be 1.3 per 100,000 with 72% of cases consisting of young boys or men [199]. Those ages 16 to 20 had the highest incidence of unexplained SCD at 0.8 per 100,000 persons per year [199]. Of the total 198 cases of unexplained SCD cases, 113 (57%) were able to be tested for genetic mutations. Of those, the authors reported a clinically relevant gene mutation in 31 (27%) of unexplained SCD cases [199]. Furthermore, 13% of the families participating which had an unexplained SCD received a clinical diagnosis of an inherited cardiovascular disease (via diagnosis in a first-degree relative) [199]. These findings are important as 40% of all cases evaluated were deemed unexplained SCD [199]. The authors also note that unexplained SCD is often attributed to cardiac arrhythmia due to ion-channel dysfunction that is not detectable in conventional autopsies [199]. Such findings may indicate a greater need for genetic testing earlier in life to identify these individuals and also included in autopsies in instances such as that of the 16 year old male in this case where the dose of caffeine alone is an insufficient explanation. Also relevant to this case is the lack of any apparent cardiac abnormalities (i.e., structural heart disease) at autopsy of the young male, which is known to occur in cases of SCD in younger individuals [198]. It is unknown whether detailed histologic examination took place at autopsy in this case which may also reveal abnormalities not apparent from macroscopic examination [198].

7.3.4. A final determination

Ultimately, the exact cause of death in the 16 year old male's case is unknown. Assuming that other potential causes such as over the counter medications, dietary supplements or prescription medications were already ruled out as contributors in this case, one is ultimately left with some likely genetic predisposition (or perhaps a combination of them) or possibly a pre-existing structural heart disease not revealed with macroscopic examination [198]. Unless genetic analyses and histologic examination were completed it ultimately leaves only speculation as to whether there was a single cause or if there was a confluence of factors that ultimately caused his death. Additional work is also needed to determine what molecular target or targets that caffeine is affecting in cases of toxicity. Ideally, an effort would be made to identify cases such as these and after a thorough examination to rule out any other potential causes, genetic analyses would take place to determine if these individuals have any mutations in certain molecular targets or metabolic enzymes that might be relevant to caffeine toxicity (e.g., COMT, CYP1A2, adenosine receptors, hERG, RyR2, etc.) and if these individuals as a group have any unique mutations (e.g., KCNQ1,

KCNH2, SCN5A, mutations indicative of long QT syndrome type I, II or III, respectively or RyR2 mutation indicative of CPVT type I but they are many more; up to 35% of cases of sudden unexplained death may be explained by cardiac channeolpathies caused by genetic mutations) that may be shared amongst them [199–201]. This is an area of research that could yield benefit and perhaps identify those in the population that are sensitive to such effects from caffeine.

7.4. Potential solutions

In cases of intentional caffeine overdose, tablets containing caffeine are typically ingested with suicidal intent. In recognition of this in the country of Sweden, sales of caffeine tablets were limited in quantity (i.e., from 100 to 250 tablets per box down to 30) in an attempt to reduce the number of intentional and fatal caffeine intoxications [100]. While the reduction suffered an initial delay, presumably due to left-over products purchased prior to enactment of the purchase restriction, from 2007 until 2009 there were no fatal intoxications attributed to caffeine [100]. However, it is important to note as the authors do that individuals may have simply turned to alternative substances to attempt suicide. Nonetheless, such data appear promising with respect to reducing the likelihood of intentional caffeine intoxication. In the United States caffeine is also included in multi-ingredient formulas used to treat migraine and other conditions, thus individuals may still have access to substances including caffeine in tablet form [176].

With respect to unintentional overdose, the United States FDA recently and prudently, banned the sale of pure, concentrated caffeine powders which have resulted in inadvertent overdoses [202]. Some understandable efforts are underway in some areas of the United States to limit the sale of energy drinks to those 18 years of age or older [160]. Perhaps one potential solution may be to restrict purchases of caffeinated energy drinks containing more than the governmental bodies' recommended 2.5–3.0 mg/kg/daily limit for children and adolescents to those ages 18 or older [25]. However, the regulation of energy drinks based upon caffeine content alone may be problematic, considering the equivalent or even greater content of caffeine available in coffee or espresso-based beverages. A potential solution may be to limit the content of caffeine in such energy drinks as it is already done for soft drinks in the United States and energy drinks in Canada [203]. Finally, recommendations by manufacturers of energy drinks to the consumer, suggesting they seek medical advice prior to use and avoid over-consumption of the product or consumption with other sources of caffeine may be prudent [203]. It has also been suggested that adolescents consume no more than 1 can (250 mL) per day in order to avoid adverse effects [193].

8. Conclusion

Caffeine is an interesting molecule with diverse physiological effects in humans. While it has a long history of consumption around the world and continues to be consumed in significant quantities there is still much to be learned about caffeine's pharmacology and toxicology in humans. The main molecular target considered today is the adenosine receptor but research continues in this area. Despite having a general understanding of the toxic and lethal doses of caffeine there is clearly a need for more data, especially with respect to determining safe doses in sensitive populations. The diagnosis of caffeine toxicity is based largely upon reported ingestion and symptoms, although serum caffeine concentrations can be obtained through quantitative chemical analysis. Caffeine's toxicological symptoms vary according to the dose and individual, with psychological side effects generally manifesting at lower dosed-intoxications and more serious side effects occurring in the cardiovascular and muscular tissues with higher doses. Treatment generally involves supportive therapy along with decontamination and increased elimination techniques, although there is no standard treatment regimen. The case of a 16 year old male, who died after

consuming several caffeine-containing beverages illustrates the need for data examining why individuals such as this have succumb to caffeine and/or caffeine along with other constituents in an energy drink, especially in light of the fact that consumption of these drinks has only increased since their introduction to the market. Looking to steps that other countries have taken in order to reduce the risk of intentional and unintentional caffeine intoxication may provide insight into how the United States and other countries may similarly implement such practices.

Conflict of interest

The author has served as a consultant to companies in the dietary supplement industry who have manufactured products containing caffeine. However, these companies would not be expected to gain financially by the work and have no knowledge of or influence over this work at the time of submission.

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