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Caffeine

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Continuing Education Activity

Caffeine is a naturally occurring central nervous system (CNS) stimulant of the methylxanthine class and is the most widely taken psychoactive stimulant globally. This drug is most commonly sourced from the coffee bean but can also be found naturally occurring in certain types of tea and cacao beans, and it is also an additive to soda and energy drinks. The primary goal of caffeine consumption is to combat fatigue and drowsiness, but there are many additional uses. This activity reviews the mechanism of action, adverse event profile, toxicity, dosing, pharmacodynamics, and monitoring of caffeine, pertinent for clinicians and other interprofessional team members where caffeine is already in use or might be necessary.

Objectives:

- Review the FDA-approved on-label indications of caffeine, as well as other non-FDA uses.
- Identify the proposed mechanism of action of caffeine.
- Summarize the contraindications and associated risks associated with caffeine use.
- Outline interprofessional team strategies for improving care coordination and communication when considering or using caffeine or controlling its use by patients to improve outcomes.

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Indications

Caffeine is a naturally occurring central nervous system (CNS) stimulant of the methylxanthine class and is the most widely taken psychoactive stimulant globally. This drug is most commonly sourced from the coffee bean but can also be found naturally occurring in certain types of tea and cacao beans. It is also an additive to soda and energy drinks. The primary goal of caffeine consumption is to combat fatigue and drowsiness, but there are many additional uses.[1]

The FDA has approved caffeine for use in the treatment of apnea of prematurity and prevention and treatment of bronchopulmonary dysplasia of premature infants.[2][3][4] Non-FDA-approved uses of caffeine include treating migraine headaches and post-dural puncture headaches and enhancing athletic performance, especially in endurance sports.[5][1] Caffeine has links with decreased all-cause mortality.[6][7] It is also under investigation for its efficacy in treating depression and neurocognitive declines, such as those seen in Alzheimer and Parkinson disease.[8][9][10]

Mechanism of Action

Caffeine's primary mechanism of action is on the adenosine receptors in the brain. As it is both fat and water-soluble, it readily crosses the blood-brain barrier, resulting in antagonism to all four adenosine receptor subtypes (A1, A2a,

A2b, A3). Specifically, the antagonism of the A2a receptor is responsible for the wakefulness effects of caffeine.[11][12]

Adenosine receptors are not limited to the CNS but are present throughout the body. In cardiac muscle, direct antagonism of receptor A1 results in positive inotropic effects. Likewise, adenosine receptor antagonism stimulates the release of catecholamines, contributing to the systemic stimulatory effects of caffeine and further stimulating cardiac inotropy and chronotropy. At the vascular level, caffeine undergoes a complex interaction to control vascular tone, which includes direct antagonism of vascular adenosine receptors to promote vasodilation, as well as stimulation of endothelial cells to release nitric oxide. This action promotes further relaxation of vascular smooth muscle cells. This vasodilation becomes counteracted by increased sympathetic tone via catecholamine release and positive cardiac inotropic and chronotropic effects, promoting vasoconstriction. As there are multiple constriction and dilatation mechanisms at work, the overall result is individualized and dependent upon caffeine dose, the frequency of use, and comorbidities such as diabetes or hypertension. Overall, caffeine seems to increase systolic blood pressure by approximately 5 to 10 mmHg in individuals with infrequent use. However, there is little to no acute effect on habitual consumers.[13][12]

Furthermore, adenosine receptor blockage stimulates respiratory drive by increasing medullary ventilator response to carbon dioxide, stimulating central respiratory drive, and improving diaphragm contractility. Caffeine increases renal blood flow, glomerular filtration, and sodium excretion resulting in diuresis. It is also a potent stimulator of gastric acid secretion and gastrointestinal (GI) motility.[12][14]

Metabolism of caffeine primarily occurs in the liver via the cytochrome P450 oxidase system, specifically enzyme CYP1A2. Metabolism results in 1 of 3 dimethylxanthine, including paraxanthine, theobromine, and theophylline, each with unique effects on the body. These metabolites are then further metabolized and excreted in the urine.[13][15]

The half-life of caffeine is approximately 5 hours in the average adult. However, multiple factors can influence metabolism. Half-life is reduced by up to 50% in smokers compared to nonsmokers. Conversely, pregnant patients, especially those in the final trimester, will demonstrate a prolonged half-life upwards of 15 hours. Newborns will also have a significantly prolonged half-life, up to 8 hours for full-term and 100 hours for premature infants, due to reduced activity of cytochrome P450 enzymes and immature demethylation pathways. Children older than nine months will have similar half-life eliminations to that of adults. Additionally, patients with liver disease or those taking cytochrome inhibitors will also experience prolonged half-lives due to reduced enzyme activity.[16][17]

Administration

Caffeine has nearly 100% oral bioavailability and is the primary route of administration. Caffeine can be sourced from coffee beans, cacao beans, kola nuts, tea leaves, yerba mate, the guarana berry, as an additive to sodas and energy drinks, or consumed as powder or tablets.[1] When taken orally, onset typically occurs in 45 to 60 minutes and lasts approximately 3 to 5 hours. Absorption is somewhat delayed when taken with food. It can be administered via the parenteral route, which is a common method when treating apnea of prematurity in newborns or post-dural puncture headaches.

Alternatively, caffeine can be absorbed rectally, insufflated, or inhaled. Consumption via insufflation or inhalation is generally a form of misuse with the intention of "getting high." These routes lead to significantly faster absorption, usually within minutes, and bypass the first-pass metabolism. Although this route can lead to a faster onset of action, multiple studies have shown lower bioavailability from inhalation of caffeine; approximately 60% to 70%. When taken via this route, the duration of action is shorter.[15][18]

Adverse Effects

As with most drugs or medications, there is a long list of adverse effects associated with their use, and caffeine is no different. The adverse effects of caffeine range from mild to severe to even fatal and are generally related to the dose consumed and an individual's sensitivity to the drug. The most common side effects are listed below. Mortality is usually associated with cardiac arrhythmia, hypotension, myocardial infarction, electrolyte disturbances, and aspiration.[19][7]

Mild

Anxiety, restlessness, fidgeting, insomnia, facial flushing, increased urination, muscle twitches or tremors, irritability, agitation, elevated or irregular heart rate, GI upset

Severe

Disorientation, hallucinations, psychosis, seizure, arrhythmias, ischemia, rhabdomyolysis

Caffeine can also cause withdrawal symptoms if habitual users abruptly stop. These symptoms usually begin 12 to 24 hours from last consumption, peak in 1 to 2 days, and may persist for up to 1 week. Withdrawal is preventable if caffeine is tapered off instead of abruptly discontinued. If symptoms do arise, they are promptly reversible by re-administration of caffeine.[20]

Lastly, when used to treat apnea of prematurity, there is evidence of an increased risk of necrotizing enterocolitis in neonates.[21]

Contraindications

Although there are no absolute contraindications to caffeine, there are some medical conditions in which caution is necessary, which includes[7][22][14][17]:

- Severe anxiety
- Cardiovascular disease or symptomatic cardiac arrhythmias
- Peptic ulcer disease or gastroesophageal reflux disease
- Hepatic impairment
- Renal impairment
- Seizures (as may lower seizure threshold)
- Pregnancy

American College of Obstetricians and Gynecologists (ACOG) considers 200 mg daily safe during pregnancy.[23] There is no evidence to suggest caffeine increases the risk of congenital malformations.[24] However, some studies have concluded that high caffeine consumption during pregnancy (more than 400 mg per day) may be associated with lower birth weights from intrauterine growth restriction, increased risk of miscarriage, but not preterm birth.[25][26] However, the evidence regarding lower birth weight and miscarriage is presently inconclusive and pending further investigation.[27] Caffeine is considered a pregnancy class C drug.[23]

Monitoring

The average dose of caffeine is 2.4 mg/kg per day for adults; however, daily doses of up to 400 mg are considered safe.[28] Consumption of 100 mg of caffeine generally increases blood levels by 5 to 6 mg/L.[29] There are reports of severe intoxication that causes altered mentation, vomiting, and hypotension at levels of 80 mg/L. The average blood level of patients who succumb to caffeine toxicity is 180 mg/L (+/- 97 mg/L).[30]

For the treatment of apnea of prematurity, caffeine is administered as a 20 mg/kg loading dose, followed by 5 to 10 mg/kg per day of caffeine citrate via enteral or parenteral routes with therapeutic index goals of 5 to 25 mg/L.[31][32]

Toxicity

Caffeine consumption is generally recognized as safe. Most substances do not require FDA approval for additive caffeine as long as it falls within safe levels dictated by the statute. The typical dose of caffeine is roughly 70 to 100 mg per drink. Although there is no specific daily allowance for caffeine, doses of up to 400 mg a day are considered safe.[33]

The exact LD50 for humans is variable and largely dependent on sensitivity to caffeine. However, it is estimated to be 150 to 200 mg/kg. There are, however, case reports of doses as low as 57 mg/kg being fatal. A toxic dose of caffeine, or a dose at which significant unfavorable side effects begin to occur, for example, tachycardia, arrhythmia, altered mentation, and seizure, is estimated to be approximately 1.2 grams, while estimates of a life-threatening dose are in the range of 10 to 14 grams.[19][34]

Ultimately, treatment is primarily supportive in cases of mild ingestions. For more severe ingestions, additional interventions may be necessary. Patients may require intubation for airway protection from vomiting or altered mental status. Benzodiazepines can be given to abort any seizures that develop. Patients may require vasopressors to combat persistent hypotension if intravenous (IV) fluid resuscitation alone fails. The first-line vasopressor should be either phenylephrine or norepinephrine. However, phenylephrine is the ideal choice due to its pure alpha agonism as well as reflex bradycardia. Magnesium and beta-blockers can be used to combat cardiac arrhythmias secondary to the hyperadrenergic response.[34] The ultra-short acting beta-1 selective blocker esmolol has been used successfully in several case reports for this indication. In the event of lethal arrhythmias, patients will require defibrillation and resuscitation per ACLS protocol.[22] Activated charcoal, intralipid infusion, and hemodialysis can help prevent further metabolism and subsequent effects of caffeine overdose.[19][35]

Enhancing Healthcare Team Outcomes

Caffeine consumption is relatively safe in limited amounts. The problem is that many people today are consuming high-energy drinks that contain massive amounts of caffeine, which can lead to complications. Today the issue of caffeine toxicity has been worsened with high-energy drinks. These concentrated caffeinated beverages are not only toxic themselves, but the problem becomes exacerbated when the individual combines caffeine use with other illicit agents, such as tobacco and alcohol. Over the past few years, there have been reports of many deaths following the consumption of such combinations.

Dealing with caffeine toxicity or side effects, or using caffeine therapeutically, requires an interprofessional healthcare team for optimal results. For therapeutic use, query the patient about other potential caffeine sources so that toxicity is not an issue with therapy. Team members are in a prime position to educate the public on the dangers of high-energy drinks and related foods. Clinicians, nursing staff, and pharmacists must be prepared to offer counsel to patients who may be overindulging in caffeine. While there are no absolute contraindications to caffeine, the public should be advised to avoid caffeine if they have cardiac disorders, panic disorder, anxiety, or elevated stress levels. An interprofessional team is the best means by which to convey this message. [Level 5]

Review Questions

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