

Caffeine - StatPearls - NCBI Bookshelf

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Continuing Education Activity

Caffeine is a naturally occurring central nervous system stimulant belonging to the methylxanthine class and is widely recognized as the most utilized psychoactive stimulant worldwide. Although this drug is most commonly sourced from coffee beans, it can also naturally occur in certain types of tea and cacao beans and as an additive to soda and energy drinks. Caffeine consumption primarily alleviates fatigue and drowsiness but has numerous additional therapeutic applications. The US Food and Drug Administration (FDA) has approved caffeine for treating apnea of prematurity. Off-label uses of caffeine include the treatment of migraines and post-dural puncture headaches, as well as enhancing athletic performance, particularly in endurance sports.

This activity centers on the mechanism of action, adverse event profile, toxicity, dosing, and monitoring of caffeine, empowering clinicians to identify potential adverse reactions, make informed prescribing decisions, and mitigate risks effectively. This activity underscores how the interprofessional healthcare team's comprehensive knowledge of caffeine's indicated and off-label uses contributes to enhanced patient outcomes.

Objectives:

- Identify appropriate indications for caffeine therapy in clinical practice, including but not limited to apnea of prematurity, migraines, and post-dural puncture headaches.
- Implement evidence-based strategies for dosing caffeine, considering individual patient characteristics and therapeutic goals.
- Apply knowledge of caffeine's mechanism of action and pharmacokinetics to make informed prescribing decisions and monitor treatment efficacy.
- Collaborate with interprofessional healthcare team members to ensure comprehensive patient care, particularly in populations with unique caffeine-related considerations, such as pregnant women and infants.

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Indications

Caffeine is a naturally occurring central nervous system (CNS) stimulant belonging to the methylxanthine class and is widely recognized as the most utilized psychoactive stimulant worldwide. Although this drug is most commonly sourced from coffee beans, it can also naturally

occur in certain types of tea and cacao beans. Moreover, the stimulant is also an additive to soda and energy drinks. Caffeine consumption primarily alleviates fatigue and drowsiness but has numerous additional therapeutic applications.

FDA-Approved Indications

The US Food and Drug Administration (FDA) has approved oral caffeine for restoring mental alertness or wakefulness in fatigue or drowsiness. The FDA has also approved intravenous (IV) caffeine for use in the treatment of apnea of prematurity. Recommendations from The Association for Professionals in Infection Control and Epidemiology, the Society for Healthcare Epidemiology, the Infectious Diseases Society of America, the American Hospital Association, and The Joint Commission Consensus endorse the use of caffeine within 72 hours after childbirth to aid extubation for the treatment of apnea of prematurity.

Off-Label Uses

IV caffeine is also used for the prevention and treatment of bronchopulmonary dysplasia in premature infants, which often coexists with apnea of prematurity. Off-label uses of caffeine include the treatment of migraines and post-dural puncture headaches, as well as enhancing athletic performance, particularly in endurance sports. Caffeine is associated with decreased all-cause mortality. Moreover, ongoing investigations are exploring its potential efficacy in treating depression and neurocognitive declines, including those observed in Alzheimer and Parkinson diseases.

According to the American Academy of Family Physicians (AAFP), the combination of acetaminophen, aspirin, and caffeine demonstrates strong evidence of effectiveness in treating acute migraines. Additionally, acute consumption of caffeine capsules significantly improves muscle strength and endurance, particularly in men. Recent meta-analyses indicate that ingesting caffeine 45 minutes before exercise improves muscle strength and endurance in men.

Mechanism of Action

Caffeine's primary mechanism of action involves its effects on adenosine receptors in the brain. Being both fat- and water-soluble component, caffeine easily crosses the blood-brain barrier and antagonizes all 4 adenosine receptor subtypes (A₁, A_{2a}, A_{2b}, and A₃). The antagonism of the A_{2a} receptor is particularly responsible for caffeine's wakefulness effects.

Adenosine receptors are not limited to the CNS but are present throughout the body. Direct antagonism of receptor A₁ in cardiac muscles 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 complex interactions to control vascular tone, including direct antagonism of vascular adenosine receptors to promote vasodilation and stimulate endothelial cells to release nitric oxide, which further relaxes vascular smooth muscle cells.

This vasodilation is counteracted by increased sympathetic tone via catecholamine release and positive cardiac inotropic and chronotropic effects, promoting vasoconstriction. Multiple mechanisms of constriction and dilation are at work, resulting in an individualized response dependent on caffeine dose, frequency of use, and comorbidities such as diabetes or hypertension. With infrequent use, caffeine appears to increase systolic blood pressure by approximately 5 to 10 mm Hg. However, little to no acute effect is observed in habitual consumers.

Furthermore, blocking adenosine receptors stimulates respiratory drive by increasing the medullary ventilatory response to carbon dioxide, enhancing central respiratory drive, and improving diaphragm contractility. Caffeine increases renal blood flow, glomerular filtration, and sodium excretion, resulting in diuresis. Additionally, caffeine is a potent stimulator of gastric acid secretion and gastrointestinal motility.

Pharmacokinetics

Absorption: Caffeine has nearly 100% oral bioavailability and is the primary route of administration. In preterm neonates, the average time to achieve peak concentration (T_{max}) after oral administration varies between 30 minutes and 2 hours.

Distribution: Caffeine is rapidly distributed to the brain. The average volume of caffeine distribution in infants (0.8-0.9 L/kg) is slightly higher than in adults (0.6 L/kg). In adults, approximately 36% of caffeine is bound to plasma proteins.

Metabolism: Caffeine is primarily metabolized in the liver via the cytochrome P450 oxidase system, specifically the enzyme CYP1A2. This metabolism results in 1 of 3 dimethylxanthines, including paraxanthine, theobromine, and theophylline, each with unique effects on the body. These metabolites are then further metabolized and excreted in the urine.

Excretion: Although the half-life of caffeine in the average adult is approximately 5 hours, multiple factors can influence the metabolism and duration. In smokers, the half-life is reduced by up to 50% compared to nonsmokers. Conversely, pregnant patients, especially in the final trimester, may experience a prolonged half-life of up to 15 hours. Newborns also have significantly prolonged half-lives—up to 8 hours for full-term infants and 100 hours for premature infants—due to reduced activity of cytochrome P450 enzymes and immature demethylation pathways. Children older than 9 months have similar half-life eliminations to adults. Additionally, patients with liver disease or those taking cytochrome inhibitors will experience prolonged half-lives due to reduced enzyme activity.

Administration

Available Dosage Forms and Strengths

Caffeine is obtainable from various sources, including coffee beans, cacao beans, kola nuts, tea leaves, yerba mate, and the guarana berry. In addition, caffeine is commonly found as an additive in sodas and energy drinks or consumed in powder or tablet form. Absorption may be slightly delayed when taken with food. The stimulant can be administered via the parenteral route, which is a standard method when treating apnea of prematurity in newborns or post-dural puncture headaches. IV formulations are available in 60 mg/3 mL caffeine citrate vials, providing an equivalent dosage of 10 mg/mL caffeine.

Alternatively, caffeine can be absorbed rectally, insufflated, or inhaled. However, consumption through insufflation or inhalation is typically considered a form of misuse aimed at achieving a "high." These routes result in much faster absorption, typically within minutes, and bypass the first-pass metabolism. Although this route can lead to a faster onset of action, multiple studies have demonstrated lower bioavailability from inhaling caffeine, approximately 60% to 70%. Consequently, when taken via these routes, the duration of action is shorter.

Specific Patient Populations

Hepatic impairment: Caffeine's product labeling does not specify dosage adjustments for individuals with hepatic impairment. However, individuals with advanced cirrhosis may experience delayed caffeine metabolism, leading to adverse drug reactions such as insomnia, nervousness, and headaches, even at intake levels that are typically well tolerated by individuals without liver disease. While caffeine may offer modest protective effects against the progression of chronic liver disease, energy drinks containing harmful supplements may contribute to liver injury.

Renal impairment: Product labeling does not specify dosage adjustments for renal impairment. Although exposure to caffeine is associated with decreased rates of acute kidney injury during the acute phase in premature neonates, this effect is not observed in term neonates. However, the impact of caffeine exposure on the severity of acute kidney injury, length of hospital stay, morbidity, or mortality remains uncertain. The optimal caffeine dosage for renal protection in neonates has yet to be determined.

Pregnancy considerations: Caffeine readily crosses the placenta. The American College of Obstetricians and Gynecologists (ACOG) considers 200 mg caffeine daily safe during pregnancy, and no evidence suggests an increased risk of congenital malformations. However, some studies have suggested that high caffeine consumption during pregnancy (more than 400 mg/d) may be associated with lower birth weights due to intrauterine growth restriction and an increased risk of miscarriage, although not preterm birth. Nonetheless, the evidence regarding lower birth weight and miscarriage is currently inconclusive and requires further investigation. Caffeine is considered a pregnancy category C drug.

Breastfeeding considerations: Caffeine is detectable in breast milk. Infants of mothers with very high caffeine intake, roughly equivalent to consuming 10 or more cups of coffee daily, may experience jitteriness and disrupted sleep patterns. Notably, mothers are suggested to limit their

caffeine intake to 300 to 500 mg daily, although European guidelines recommend a likely safe level of 200 mg. Lower intake levels are advisable for mothers of preterm infants due to slower caffeine metabolism in these infants. Additionally, consuming more than 450 mL of coffee daily may decrease iron levels in breast milk, potentially leading to mild iron deficiency anemia in some breastfed infants.

Pediatric patients: Caffeine citrate injection is FDA-approved for treating apnea of prematurity. According to the manufacturing label, the recommended dosages for this condition are outlined in the table below.

Older patients: According to a cohort study, coffee and caffeine consumption exhibited a notable correlation with a reduced risk of dementia in a dose-dependent manner, especially among men.

Adverse Effects

As with many drugs or medications, a wide array of adverse effects is associated with caffeine use. These effects vary from mild to severe and, in some cases, can be fatal, depending on the dose consumed and an individual's sensitivity to the drug. The most frequently reported adverse effects are outlined below. Mortality is usually associated with cardiac arrhythmia, hypotension, myocardial infarction, electrolyte disturbances, and aspiration.

Mild Adverse Effects

Mild adverse effects of caffeine include anxiety, restlessness, fidgeting, insomnia, facial flushing, increased urination, irritability, muscle twitches or tremors, agitation, tachycardia or irregular heart rate, and gastrointestinal irritation.

Severe Adverse Effects

Severe adverse effects may include disorientation, hallucinations, psychosis, seizures, arrhythmias, ischemia, and rhabdomyolysis. Additionally, caffeine can lead to withdrawal symptoms if habitual users abruptly cease consumption. These symptoms typically begin 12 to 24 hours after the last intake, peak in 1 to 2 days, and may endure for up to 1 week. However, withdrawal can be avoided by gradually tapering off caffeine rather than abruptly discontinuing it. In the event of symptoms, they can be promptly reversed by re-administering caffeine.

Lastly, when caffeine is used to treat apnea of prematurity, it is normal to observe evidence of an increased risk of necrotizing enterocolitis in neonates. According to the 2023 guidelines from the American College of Cardiology (ACC), American Heart Association (AHA), American College of Clinical Pharmacy (ACCP), and Heart Rhythm Society (HRS), advising patients with atrial fibrillation to abstain from caffeine to prevent atrial fibrillation episodes lacks supporting evidence. However, caffeine avoidance may alleviate symptoms in patients who find that caffeine exacerbates their atrial fibrillation symptoms.

Current research does not preclude the possibility of individual-specific idiosyncratic reactions between caffeine and atrial fibrillation. Additionally, caffeine may mimic symptoms such as palpitations or enhance awareness of heart rhythm irregularities. A systematic study supports sleep hygiene recommendations to avoid substantial caffeine intake at least 6 hours before bedtime due to its significant disruptive effects on sleep.

Drug-Drug Interactions

The CYP1A2 enzyme metabolizes caffeine and functions as a competitive inhibitor of this enzyme. Consequently, caffeine can interact with various psychiatric medications, including antidepressants, antipsychotics, anxiolytics, and sedatives. As CYP1A2 metabolizes tizanidine, concurrent use with caffeine should be avoided. Additionally, bupropion can lower the seizure threshold, so caution should be exercised when using it concurrently with caffeine. Furthermore, the sedative effects of alcohol and the psychoactive stimulant effects of caffeine can mask their respective influences on both sleep quantity and sleep quality.

Contraindications

Although no absolute contraindications to caffeine are recognized, caution is necessary in certain medical conditions, including:

- Documented hypersensitivity
- Severe anxiety
- Cardiovascular disease or symptomatic cardiac arrhythmias
- Peptic ulcer disease or gastroesophageal reflux disease
- Hepatic impairment
- Renal impairment
- Seizures (as caffeine may lower seizure threshold)
- Pregnancy [\[45\]](#)[\[46\]](#)[\[47\]](#)[\[48\]](#)

Monitoring

The average dose of caffeine for adults is 2.4 mg/kg/d; however, daily doses of up to 400 mg are considered safe. A 100 mg dose of caffeine generally increases blood levels by 5 to 6 mg/L. Severe intoxication, characterized by altered mentation, vomiting, and hypotension, has been reported at levels of 80 mg/L. The average blood level in patients who succumb to caffeine toxicity is 180 mg/L (± 97 mg/L). For the treatment of apnea of prematurity, caffeine is administered with therapeutic index goals of 5 to 25 mg/L.

Toxicity

Signs and Symptoms of Overdose

Caffeine consumption is generally regarded as safe. Additive caffeine in most substances does not necessitate FDA approval as long as consumption remains within safe levels stipulated by the statute. A typical dose of caffeine is around 70 to 100 mg per drink. While there is no recommended daily allowance for caffeine, doses of up to 400 mg/d are deemed safe.

The exact LD₅₀ for humans varies and largely depends on individual sensitivity to caffeine. However, the estimated LD₅₀ is between 150 and 200 mg/kg. Case reports indicate that doses as low as 57 mg/kg have resulted in fatalities. A toxic dose of caffeine, where significant adverse effects such as tachycardia, arrhythmia, altered mentation, and seizures may occur, is estimated to be around 1.2 g. The estimates of a life-threatening dose of caffeine range from 10 to 14 g.

Management of Overdose

The treatment for mild ingestions primarily involves supportive care. However, in cases of more severe ingestions, additional interventions may be necessary. Patients may require intubation to protect the airway from vomiting or altered mental status. Benzodiazepines can be administered to abort any seizures that develop. If IV fluid resuscitation fails to address persistent hypotension, patients may need vasopressors. Phenylephrine or norepinephrine is typically the first-line vasopressor, with phenylephrine being preferable due to its α-agonism and reflex bradycardia.

Magnesium and β-blockers can combat cardiac arrhythmias secondary to the hyperadrenergic response. The ultra-short-acting β₁-selective blocker esmolol has been used successfully in several case reports for this indication. In the case of lethal arrhythmias, patients will require defibrillation and resuscitation according to advanced cardiac life support protocols. Additionally, activated charcoal, intralipid infusion, and hemodialysis can aid in preventing further metabolism and subsequent effects of caffeine overdose.

Enhancing Healthcare Team Outcomes

Caffeine consumption is generally considered safe in moderate amounts. However, the prevalence of high-energy drinks containing excessive caffeine levels has escalated the problem of caffeine toxicity. These concentrated caffeinated beverages pose a significant risk on their own, but the danger escalates when combined with other illicit substances such as tobacco and alcohol. In recent years, numerous fatalities have been reported following the ingestion of such combinations.

Addressing caffeine toxicity or adverse effects necessitates the collaboration of an interprofessional healthcare team to achieve optimal outcomes. In cases where caffeine is used for apnea of prematurity, consultation with a pediatrician and admission to a neonatal intensive care unit may be necessary. When using caffeine therapeutically, it is essential to inquire about

other potential sources of caffeine to prevent toxicity. Healthcare team members are well-positioned to educate the public about the risks associated with high-energy drinks and related products. Clinicians, nursing staff, and pharmacists should be ready to offer counseling to patients who may be consuming excessive amounts of caffeine. While no absolute contraindications to caffeine exist, patients with cardiac disorders, panic disorder, anxiety, or elevated stress levels should be advised to avoid caffeine. An interprofessional healthcare team is well-equipped to educate patients appropriately in this regard.

Review Questions

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Tables

Table. Caffeine Citrate Dosages for Apnea of Prematurity

Doses	Dose of caffeine citrate (mg/kg)	Route (IV: A syringe infusion pump)	Frequency
Loading dose	20	IV (over 30 minutes)	One time
Maintenance dose	5	IV (over 10 minutes) or orally	Every 24 hours (beginning 24 hours after the loading dose)