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Caffeine Toxicity

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Introduction

Caffeine is a stimulant that has been utilized globally for centuries secondary to its ability to improve mental alertness. As many as 85% of Americans consume caffeine daily with the average cup of coffee containing anywhere from 40 to 150 mg of caffeine.[1] Caffeine can be found in many over-the-counter preparations (energy drinks, appetite suppressants, stimulants, exercise supplements, decongestants, bronchodilators, and mental stimulants), increasing the risk of toxicity with inadvertent overuse or severe toxicity with an intentional overdose.[2] Lethal doses of caffeine have been reported at blood concentrations of 80 to 100 micrograms/ml which can be reached with ingestion of approximately 10 grams or greater.[3][4][5][6][7]

Etiology

Lethal overdoses of caffeine in adults are rare but when encountered are commonly caused by an intentional overdose of medications.[8][9][10] Conversely, caffeine toxicity in children is typically caused by accidental ingestion.[11] Toxic ingestions can be seen after ingestion of energy drinks but are rarely seen from ingestion of coffee or tea secondary to the excessive amount of fluid that would have to be ingested to reach toxic levels.[12] Over-the-counter drugs containing large doses of caffeine purchased for their stimulant properties can also complicate caffeine exposure. Some examples include health food products, diet aids decongestants, bronchodilators, or stay-awake pills.[13]

Epidemiology

In 2016 there were 3702 caffeine related exposures reported to Poison Control Centers in the United States, with an equal ratio of pediatric and adult cases. Of those cases, 846 required treatment at a medical facility and there were 16 major outcomes. There have been several caffeine-related deaths reported in case studies.[12]

Pathophysiology

Due to caffeine's ability to affect a variety of different receptors, the side effects of caffeine overdose can be profound. Caffeine is a natural alkaloid methylxanthine that acts as a nonselective antagonist of adenosine receptors, with A1 antagonism triggering seizures and A2 antagonism triggering cerebral and coronary vasoconstriction. Caffeine also inhibits phosphodiesterase, resulting in increased intracellular cyclic AMP and intracellular calcium levels. Caffeine can stimulate the release of catecholamines, especially noradrenaline, with beta 1 agonist activity resulting in tachycardia and beta 2 agonist activity resulting in peripheral vasodilation and hypotension. [14][10][4][15] Caffeine also sensitizes dopamine receptors and is a competitive antagonist of benzodiazepine receptors. Furthermore, caffeine increases renin excretion, resulting in initial hypertension, sodium retention, and water retention. [6][16][17][10]

Toxicokinetics

Caffeine is rapidly and nearly completely (up to 90%) absorbed by the stomach with peak plasma concentrations occurring within 20 to 40 minutes.[18] As a result, toxic levels can be reached quickly and last for prolonged periods of time secondary to caffeine's 3- to 10-hour half-life. The liver metabolizes caffeine via N-demethylation, acetylation, and oxidation. Other substances that

use these same pathways, such as alcohol or medications, can prolong the half-life of caffeine by approximately 72%.[9][6]

History and Physical

Physical exam findings characteristic for caffeine toxicity include fever, tachycardia or bradycardia, and hypertension early on followed by hypotension. Pupils may demonstrate mydriasis. Muscles may be rigid and deep tendon reflexes may be accentuated (hyperreflexia). A neurologic exam may demonstrate altered mentation, agitation, delusional thought, hallucinations, seizures or even focal neurologic findings thought to be due to ischemia from vasoconstriction. The patient is commonly nauseated and will frequently have vomiting. [16][19][20]

Evaluation

Routine serum laboratory evaluations can be useful in drug overdose cases, especially in the setting of unstable vital signs, seizures or altered sensorium. Serum caffeine levels can guide prognosis and therapy. Although not available in all hospitals, serum caffeine levels are generally obtained with an immunoassay.[21][22] Lethal blood levels are typically above 80 to 100 mg/L, although one case occurred at 15 mg/L.[6] A venous blood gas may demonstrate anion gap metabolic acidosis which can be severe. Lactate levels are commonly elevated. Caffeine toxicity can result in hypokalemia, hypocalcemia, hyponatremia, and hyperglycemia. It is also important to obtain serum myoglobin and creatine kinase levels to monitor for rhabdomyolysis. An electrocardiogram may demonstrate tachycardia, ST-segment depressions, or T-wave inversions. Cardiac monitoring allows evaluation of heart rate and early recognition of dysrhythmias such as ventricular ectopy or fibrillation.[4][16][10][19]

Treatment / Management

Fatal caffeine overdose is relatively uncommon, and treatment data is limited to case reports. The primary treatment for minor caffeine ingestion is supportive. Hydration may be oral in minor cases, yet severe cases benefit from intravenous (IV) hydration. Beta-blockade with esmolol is useful for tachycardia. Procainamide, lidocaine or bicarbonate have also been utilized for treatment of tachy-dysrhythmias.[23] Vasopressors, such as vasopressin or phenylephrine, can be used to maintain blood pressure (goal mean arterial pressure greater than 65 mm Hg) without worsening tachycardia.[15] Activated charcoal can bind caffeine if the ingestion is recent, and repeated doses can help diminish serum levels via the enterohepatic circulation. Hemodialysis has been effective in severe, life-threatening caffeine ingestions. Caffeine exhibits ideal characteristics to be dialyzed, including low protein binding (36%), low molecular size (194), and a small volume of distribution (0.6 to 0.8 L/kg). Imminent cardiac arrest in caffeine toxicity should prompt intra-lipid therapy to scavenge the free serum caffeine.[24][16]

Differential Diagnosis

- Atrial fibrillation/flutter
- Carbon monoxide toxicity
- Cyanide toxicity
- Delirium tremens (DTs)
- Diabetic ketoacidosis
- Disulfiram toxicity
- Intracranial hemorrhage
- Iron toxicity

- Monoamine oxidase inhibitor toxicity
- Multifocal atrial tachycardia
- Polysubstance overdose
- Septic shock
- Status epilepticus
- Theophylline toxicity
- Thyrotoxicosis
- Ventricular fibrillation
- Ventricular tachycardia

Prognosis

There are relatively few deaths reported from caffeine overdose; however, prognosis largely depends on how quickly treatment is implemented.[12] In cases of severe caffeine overdose, the prognosis is directly correlated with the timeliness of caffeine removal from the bloodstream using hemodialysis or intralipid emulsion therapy.[16]

Complications

Complications of caffeine overdose include seizure, neurologic changes, tachy-dysrhythmia, ECG changes, hypokalemia, hyperglycemia, and an anion gap metabolic acidosis secondary to lactic acidosis. Severe cases can result in acute kidney injury, rhabdomyolysis, and even cardiac arrest.[7][20]

Postoperative and Rehabilitation Care

Secondary to the relatively short half-life of caffeine, patient's will often quickly return to baseline as caffeine levels trend down. Neurologic and cardiac changes have been reported to resolve spontaneously as caffeine is excreted from the body. All electrolyte abnormalities should be corrected and are unlikely to reoccur once caffeine levels are normalized.[25]

Consultations

There is no established standard of care or treatment plan for caffeine overdose, but poison control consultation is an excellent resource when managing these types of cases. Nephrology will need to be consulted for severe caffeine overdoses that require hemodialysis.[15][23][14][17] Cardiology may also need to be consulted for associated dysrhythmias. These patients will likely need to be admitted to the intensive care unit (ICU) and may benefit from consulting critical care.

Deterrence and Patient Education

Caffeine is easily accessible as an over-the-counter medication and as a component in several products.[2] Patients should be cautioned that caffeine can affect a variety of receptors and the side effects can be profound. Toxic results can be reached quickly and results in significant morbidity and mortality if not treated quickly.[9][6]

Pearls and Other Issues

- In cases of sympathomimetic toxidrome of unknown cause, it is important to think of caffeine toxicity, especially in the setting of hypotension, because levels can be measured and specific therapy with activated charcoal, hemodialysis or even intralipid can be instituted.
- Caffeine overdose does not have an established standard of care treatment plan, but toxic

serum caffeine levels can be successfully reversed when recognized and treated early.

- Caffeine is available over the counter and can quickly reach toxic levels when taken in excess.
- Seizures are commonly seen in toxic caffeine overdose.
- Beta blockers are the first line in treating the tachy-dysrhythmias associated with caffeine overdose.

Enhancing Healthcare Team Outcomes

The management of a caffeine overdose requires a consolidated approach by various healthcare providers including nursing staff, phlebotomy, pharmacy, toxicology, nephrology and possibly physicians from other specialties. Morbidity and mortality can be high if caffeine overdose is not recognized and treated early. The emergency medicine physician is responsible for stabilizing the patient and coordinating the patient's care while in the emergency department. Some of the responsibilities of the emergency physician include:

- Ordering drug levels in blood and or urine
- Monitor the patient for signs and symptoms of respiratory depression, cardiac arrhythmias, electrolyte abnormalities and seizures
- Performing various maneuvers to help limit absorption of the drug in the body
- Consult with poison control and pharmacy about the use of activated charcoal, benzodiazepines, supplemental potassium, and esmolol
- Consult with a toxicologist and nephrologist on further management, which may include dialysis
- Consult with the intensivist about ICU care and monitoring while in hospital

Patients need continued care from the moment they enter the emergency department until the time of discharge and beyond. If it is determined that the patient intentionally overdoses then a mental health provider should be consulted once the patient has recovered medically.

Outcomes

The outcomes after caffeine toxicity are excellent. Mortality is very rare for patients who seek treatment. Those who do not seek treatment or the treatment is delayed may develop seizures, arrhythmias or even aspirate the vomitus. Over the past decade, less than 3 dozen deaths have been reported. For those who survive, there are no residual sequelae.[26] Level III

Questions

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