Teaching Rounds in Cardiac Electrophysiology

Electrocardiogram Abnormalities of Caffeine Overdose

Carly Fabrizio, DO; Michael Desiderio, DO; Robert F. Coyne, MD

Caffeine is a widely popular, naturally occurring plant alkaloid that is classified as a methylated xanthine derivative. It is found in a variety of products, most notably coffee, carbonated beverages, and so-called energy drinks. Previous studies have confirmed that typical caffeine consumption is not generally associated with an increased risk of arrhythmias.1 Even at moderate doses (defined as <6 cups of coffee daily), caffeine is well tolerated, and there is little evidence to support that at this dosage it is proarrhythmic.1 However, intake of unusually large amounts of caffeine, where quantities are generally >10 g, has been associated with tachydysrhythmias, including organized supraventricular tachycardia, ventricular tachycardia, and ventricular fibrillation (VF). Because of the increasing popularity of caffeinated energy drinks, there is an increased risk for caffeine toxicity, and as a result, the clinical entity of acute caffeine toxicity may become a more common pathology. Therefore, it is important to not only recognize the effects of caffeine on the cardiovascular system at toxic doses but also to be aware of management strategies.

See Editor’s Perspective by Asirvatham and Stevenson

Case

A 29-year-old female patient with a history of severe depression and prior suicide attempts presented to the Emergency Department after ingestion of ≈36 to 40 g of caffeine. Before arrival, she admitted to taking 180 to 200 pills of NoDoz brand caffeine, each pill containing ≈200 mg of caffeine. She denied taking any additional prescription medications or substances other than the caffeine pills.

On presentation to the emergency room, the patient had sinus tachycardia with rates between 160 and 180 beats/min, mild hypotension with a blood pressure in the 90 mm Hg systolic range, tachypnea of 25 to 30 breaths/min, and an oxygen saturation of 98% on 100% FiO2 via Ventimask. During the initial assessment, the patient lost consciousness, with seizure-like activity prompting treatment with 2 mg intravenous lorazepam. The patient was placed on a cardiac monitor, requiring immediate initiation of advanced cardiovascular life support, inclusive of multiple external defibrillations, intubation, and IV epinephrine per advanced cardiovascular life support protocol. Resuscitation efforts were administered for ≈1 hour during which time the patient’s rhythm alternated between polymorphic ventricular tachycardia or ventricular fibrillation and brief periods of sinus tachycardia or atrial fibrillation. Additional treatment modalities included a total of 5 amps of sodium bicarbonate, 2 g of intravenous magnesium sulfate, 2 intralipid infusions (115 mL total), 150 mg intravenous amiodarone, and activated charcoal via an orogastric tube. Intravenous norepinephrine was required to maintain mean arterial pressures above 65 mm Hg. Ultimately, the addition of an esmolol infusion led to stabilized rhythms of supraventricular tachycardia (Figure 3) with episodes of nonsustained ventricular tachycardia that did not require further defibrillation or cardiopulmonary resuscitation.

Laboratory obtained during the resuscitation revealed profound and ongoing metabolic acidosis. Arterial blood gas demonstrated a pH 6.94, Pco2 44 mm Hg, Po2 408 mm Hg, and HCO3 9.5 mmol/L. Additional serum values included lactate 29.4 mmol/L, sodium 144 mmol/L, potassium 3.3 mmol/L, bicarbonate 10 mmol/L, blood urea nitrogen 17 mg/dL, creatinine 1.0 mg/dL, calcium 10.3 mg/dL, and magnesium 2.6 mg/dL. Urine toxicology was subsequently reported negative for amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opioids, phencyclidine, and methadone. Serum toxicology was unremarkable for salicylate, acetaminophen, and ethanol levels.

Given the patient’s severe acidosis, hemodynamic, and cardiovascular instability, the decision was made to initiate emergent continuous veno-venous hemodialysis. After 4 hours of hemodialysis, the patient remained in sinus rhythm with a rate of 80 beats/min, QTc of 455 ms, and slightly prolonged PR interval of 217 ms (Figure 4). She was admitted to the cardiac care unit, weaned from norepinephrine support after 24 hours, and extubated 48 hours later. No further arrhythmias occurred after completion of the hemodialysis. Although caffeine levels were sent before dialysis, lipemic samples because of intralipid infusions prohibited analysis. However, a caffeine level obtained ≈24 hours after dialysis was 33 μg/mL, well above the toxic threshold of the laboratory. An echocardiogram obtained ≈12 hours after the patient was stabilized demonstrated a structurally normal heart. An EKG obtained 5 days after admission was within normal limits (Figure 5). The patient was ultimately admitted to the inpatient psychiatric facility.

Discussion

Caffeine has a half-life of 2 to 12 hours, is nearly 100% bioavailable, and reaches maximal concentrations in the body...
within an hour of ingestion. It has a relatively low volume of distribution and low plasma protein binding. The effects of caffeine on the cardiovascular system are summarized in Table. Caffeine is a nonselective competitive antagonist of adenosine receptors (A<sub>1</sub> and A<sub>2A</sub>), which are found on the myocardium and coronary endothelium. Antagonism of these receptors results in decreased heart rate and positive chronotropic and dromotropic effects. Caffeine also acts as a phosphodiesterase inhibitor to cause significant inotropic effects via the calcium-induced calcium release process. As caffeine is metabolized in the liver, it is converted to theophylline, which in turn may cause adverse cardiac effects at high levels through blockade of adenosine receptors, resulting in increased adrenergic activity and increased catecholamine release.<sup>2</sup>

Caffeine toxicity also precipitates hypotension via direct and indirect mechanisms on the vascular smooth muscle cells. Caffeine directly inhibits myosin light chain kinase and

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**Figure 1.** Polymorphic ventricular tachycardia (VT) revealed during the initial signs of hemodynamic compromise.

**Figure 2.** Degeneration into ventricular fibrillation (VF) and subsequently into hemodynamic collapse.
indirectly activates the nitric oxide synthase enzyme, which leads to vasodilation. Furthermore, the blockade of adenosine receptors increases catecholamine release, stimulating β-1 and β-2 receptors. Beta-1 receptor stimulation leads to tachy- dysrhythmias, incomplete diastolic filling times, decreased cardiac output, and ultimately hypotension. Stimulation of β-2 receptors on the peripheral vasculature adds to the vasodilatory effects.

Currently, there is no standardized management for caffeine overdose. The literature consists of widely different treatment strategies that vary on a case-to-case basis. Effective management should address prevention of further metabolism, the overwhelming adrenergic surge, and the multifactorial etiologies of caffeine-induced hypotension. Blockade of the hyperadrenergic response with short acting B1 antagonists, such as esmolol, has led to successful outcomes. Activated charcoal, intralipid...

Figure 3. Following initiation of advanced cardiovascular life support (ACLS) protocol, intralipid infusion, amiodarone, magnesium, and finally, esmolol intravenous drip, the rhythm stabilized to supraventricular tachycardia (SVT) with diffuse ST-T wave abnormalities.

Figure 4. Electrocardiogram obtained after 4 hours of hemodialysis demonstrating normal sinus rhythm with a first degree atrioventricular nodal block.
infusion, and subsequent hemodialysis are all useful interventions that prevent further caffeine metabolism and subsequent systemic effects. Intravenous fluid resuscitation with isotonic fluid can be administered to treat the hypotension. Additional vasopressor support may also be needed. Alpha-adrenergic receptor stimulation increases vascular tone. Phenylephrine and norepinephrine can be used to obtain α-1 agonism to improve blood pressure. Phenylephrine, in particular, is beneficial in that it is both a potent alpha agonist and causes reflex bradycardia to promote hemodynamic stability. In summary, the patient experienced multiple episodes of ventricular tachyarrhythmias/fibrillation in the setting of isolated massive caffeine overdose. The ventricular arrhythmias were a result of caffeine toxicity on the cardiovascular system because of adenosine antagonism, endogenous catecholamine release, and phosphodiesterase inhibition, leading to increased cAMP availability. Management should focus on blocking the hyperadrenergic response with a short-acting β1-antagonist, removal of excess caffeine using activated charcoal, intralipid infusion and hemodialysis, and supporting hemodynamics with intravenous fluid resuscitation and vasopressors, such as phenylephrine or norepinephrine.

Table. Effects of Caffeine on the Cardiovascular System

<table>
<thead>
<tr>
<th>Location</th>
<th>Receptor</th>
<th>Mechanism</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium</td>
<td>A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Nonselective competitive antagonism</td>
<td>(+) Chronotropy</td>
</tr>
<tr>
<td></td>
<td>β&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Stimulation of sympathetic NS</td>
<td>Decreased CO</td>
</tr>
<tr>
<td>PDE</td>
<td>Nonselective antagonism</td>
<td>(+) Inotropy</td>
<td></td>
</tr>
<tr>
<td>Coronary endothelium</td>
<td>A&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>Nonselective competitive antagonism</td>
<td>(+) Coronary vasoconstriction</td>
</tr>
<tr>
<td>Vascular smooth muscle</td>
<td>MLCK</td>
<td>Direct inhibition, increases MLCP</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>β&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Stimulation of sympathetic NS</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Endothelium</td>
<td>Ryanodine</td>
<td>Production of NO</td>
<td>Vasodilation</td>
</tr>
</tbody>
</table>

A indicates adenosine; β, beta; CO, cardiac output; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; NO, nitric oxide; NS, nervous system; and PDE, phosphodiesterase.

Disclosures

None.

References

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