Myocardial Ischemia Secondary to Synthetic Cannabinoid (K2) Use in Pediatric Patients

Bradley C. Clark, MD1,2, Justin Georgekutty, MD1,2, and Charles I. Berul, MD1,2

K2 is a synthetic cannabinoid that has potential cardiovascular side effects, including myocardial ischemia, myocardial infarction, and arrhythmias. Cardiac testing of pediatric patients is often not performed owing to a lack of symptomatology. We report a series of pediatric patients with concern for myocardial ischemia temporally associated with K2 exposure. (J Pediatr 2015; - - - -).

Although epidemiologic data are limited, the reported prevalence of synthetic cannabinoid (K2, spice) ranges between 6.5% and 12.6% in adolescents and adults in the US and United Kingdom.1 Synthetic cannabinoids are more attractive than cannabis, owing to ease of purchase as well as increased odds of negative urine and blood testing. K2 has multiple known side effects, and serious events, including ischemic stroke, have been reported.2 Although there are reports of adverse cardiovascular effects secondary to cannabis or synthetic cannabinoid use, including myocardial infarction (MI), arrhythmias, and sudden death in adults,3-9 data on the cardiac effects of K2 in pediatrics is limited.10-12 We report a series of pediatric patients who were seen at a tertiary care center over a 2-year period with evidence of varying degrees of myocardial injury secondary to the use of K2.

The Children’s National Health System (CNHS) is a tertiary pediatric care center in Washington, DC that sees more than 100,000 visits to the emergency room (ER) annually. After Institutional Review Board approval was obtained from CNHS, the electronic medical record was queried for a combination of K2 use, ST segment changes, and elevated troponin levels. Individual charts were then reviewed to identify patients who used K2 and underwent evaluation for cardiac injury, which included electrocardiogram (ECG), echocardiogram, and laboratory testing. Each ECG represents an official reading from an attending pediatric cardiologist at CNHS.

Case 1

A 15-year-old previously healthy male was brought to the ER secondary to altered mental status. On later questioning, he admitted frequent K2 smoking, including smoking before presentation to the ER. He denied any chest pain, shortness of breath, or palpitations. ECG on admission showed ST elevation in the lateral leads, T wave inversions in the inferior leads, and left ventricular hypertrophy (LVH) based on voltage criteria (Figure 1, A). Laboratory testing was notable for an elevated troponin I level at 0.16 ng/mL (normal, <0.1 ng/mL) with normal creatine kinase (CK), CK-MB, and serum and urine drug screening. An echocardiogram revealed normal intracardiac anatomy, normal coronary artery origins, normal biventricular function, no wall motion abnormalities, and no evidence of pericardial effusion. The patient was admitted overnight for observation, and demonstrated a return of troponin I level to normal (0.03 ng/mL) and improved ST segments and T wave inversions (Figure 1, B). He was recently evaluated for mild hypertension in the setting of an elevated body mass index. An ECG obtained during that visit was unchanged from his discharge study. He was advised to lose weight.

Case 2

A 16-year-old healthy male was brought to the ER with altered mental status. He reported smoking K2 (“scooby”), but denied any other drug use. He denied chest pain, shortness of breath, palpitations, or dizziness. An ECG was obtained which showed ST elevation in an anterolateral injury pattern with T wave inversions (Figure 2; available at www.jpeds.com). Laboratory testing was notable for a normal troponin I level (0.03 ng/mL) and positive urine drug screen for marijuana. An echocardiogram revealed normal intracardiac anatomy, normal coronary artery origins, normal biventricular function, no wall motion abnormalities, and no evidence of a pericardial effusion. He was monitored in the ER until his mental status returned to baseline and was discharged to home with a plan for outpatient cardiology follow-up. He has not followed up to date.

CK Creatine kinase
CNHS Children’s National Health System
ECG Electrocardiogram
ER Emergency room
LVH Left ventricular hypertrophy
MI Myocardial infarction
THC Delta-9-tetrahydrocannabinol

CRP 5.2.0 DTD ▪ YMPD7591_proof ▪ 25 June 2015 ▪ 2:22 pm ▪ ce KL
Case 3

A 17-year-old male with a past medical history of impulse control disorder, depression, developmental delay, and attention deficit hyperactivity disorder presented to the ER with altered mental status and homicidal ideation. He reported smoking 4 cigarettes containing unknown substances, but there was a strong suspicion for K2 ingestion. He had reported a history of chest pain, which had resolved at the time of presentation. His ECG revealed sinus tachycardia, with ST elevation more pronounced in V2 and V3 (Figure 3, A; available at www.jpeds.com); there was evidence of RSR’ (right ventricular conduction delay) in lead V1 initially concerning for possible Brugada syndrome, but no further workup was done in the absence of previous symptoms and family history. Troponin I level was elevated at 0.39 ng/mL, but normalized within 24 hours. A urine drug screen at admission was negative. An echocardiogram showed normal intracardiac anatomy, normal coronary artery origins, normal biventricular function, no wall motion abnormalities, and no evidence of pericardial effusion. The patient was discharged from the medical service at 36 hours after presentation with an ECG showing ST elevation, though decreased from that seen at presentation (Figure 3, B). One month later, the patient presented to the ER for an unrelated complaint, at which time a repeat ECG showed no evidence of ST changes.

Additional Cases

Five patients in addition to the 3 case report patients who presented for evaluation after using K2 had ECG changes concerning for ischemia with normal serum markers (Table). All of the patients were adolescent males exhibiting a variety of symptoms at presentation, including chest pain, shortness of breath, syncope, and/or palpitations. Evaluation included ECG, echocardiogram, and laboratory testing. The majority were observed overnight and discharged home the next day. In 1 patient, acute appendicitis was found incidentally on presentation,
# Table
Clinical information, ECG findings, laboratory and echocardiogram results for all patients with ECG abnormalities in the setting of K2 usage, both with and without abnormal serum markers

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex</th>
<th>Signs and symptoms</th>
<th>Timing of K2 use</th>
<th>ECG findings</th>
<th>Laboratory test results</th>
<th>Echocardiography findings</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 M</td>
<td>AMS</td>
<td>Day of presentation</td>
<td>Initial: NSR, LVH, ST flattening in the lateral leads, T wave inversion in inferior leads</td>
<td>Troponin I 0.16 ng/mL on admission, negative at discharge</td>
<td>Normal</td>
<td>Observed inpatient; discharged home next day</td>
<td></td>
</tr>
<tr>
<td>16 M</td>
<td>AMS</td>
<td>Day of presentation</td>
<td>Initial: NSR, LVH, ST elevation in precordial leads, T wave inversion in lead III</td>
<td>Troponin I negative × 1</td>
<td>UDS: positive for MJ</td>
<td>Normal</td>
<td>Observed in ER until returned to baseline mental status; did not attend outpatient cardiology follow-up</td>
</tr>
<tr>
<td>17 M</td>
<td>AMS, homicidal ideation, chest pain</td>
<td>Day of presentation</td>
<td>Initial: sinus tachycardia, possible left atrial enlargement, ST elevation; consider anterolateral injury or infarct, ST more elevated in V2-V3</td>
<td>Troponin I 0.39 ng/mL on admission, negative at discharge</td>
<td>UDS: negative</td>
<td>Normal</td>
<td>Observed inpatient for 36 hours and transferred to psychiatry</td>
</tr>
</tbody>
</table>

### Additional cases

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Signs and symptoms</th>
<th>Timing of K2 use</th>
<th>ECG findings</th>
<th>Laboratory test results</th>
<th>Echocardiography findings</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 M</td>
<td>Shortness of breath, labored respirations</td>
<td>Day of presentation</td>
<td>Initial: NSR, LVH, ST flattening in lead III, ST elevation in septal leads</td>
<td>Troponin I negative × 3</td>
<td>UDS: negative</td>
<td>Normal</td>
</tr>
<tr>
<td>15 M</td>
<td>Palpitations, dizziness, weakness</td>
<td>Day of presentation</td>
<td>Initial: intermittent ectopic atrial rhythm, ST elevation in leads II, III, and aVF</td>
<td>Troponin I negative × 2</td>
<td>UDS: negative</td>
<td>Normal</td>
</tr>
<tr>
<td>18 M</td>
<td>Chest and back pain</td>
<td>2-3 days before presentation</td>
<td>Initial: NSR; RSR' in V1, J point elevation in precordial leads consistent with early repolarization</td>
<td>Troponin I negative × 1</td>
<td>Abdominal ultrasound: acute appendicitis UDS: positive for MJ</td>
<td>Normal</td>
</tr>
<tr>
<td>16 M</td>
<td>Seizure</td>
<td>Day of presentation</td>
<td>Initial: sinus rhythm with marked SA, ST elevation in leads I and aVF</td>
<td>Troponin I: NA ETOH: positive Elevated CK UDS: positive for MJ</td>
<td>NA</td>
<td>Observed inpatient; discharged home next day</td>
</tr>
<tr>
<td>16 M</td>
<td>Syncope, palpitations</td>
<td>Day of presentation</td>
<td>Initial: sinus rhythm with SA, leftward axis; early repolarization; nonspecific ST-T changes</td>
<td>Troponin I: NA</td>
<td>UDS: positive for TCA</td>
<td>NA</td>
</tr>
</tbody>
</table>

M, male; AMS, altered mental status; NSR, normal sinus rhythm; UDS, urine drug screen; MJ, marijuana; BNP, brain natriuretic peptide; SA, sinus arrhythmia; ETOH, ethanol; TCA, tricyclic anti-depressant; NA, not applicable.
and he underwent laparoscopic appendectomy without event.

**Discussion**

The main psychoactive component in synthetic cannabinoids is delta-9-tetrahydrocannabinol (THC). The cardiac effects of THC, both natural and synthetic, involve 2 main receptors, CB1 and CB2, located in the myocardium, coronary endothelium, and peripheral vasculature, as well as multiple other organ systems throughout the body. CB1 receptor activity mediates negative inotropy in the myocardium via inhibition of norepinephrine release and stimulates vasodilation of the coronary endothelial vasculature. CB2 receptors are located in multiple aspects of the cardiovascular system, including myocardium, coronary artery endothelium and smooth muscle cells, myofibroblasts, and cardiomyocytes, and are thought to blunt the inflammatory response and to protect against coronary reperfusion injury after an ischemic insult. Although synthetic cannabinoids have shown some beneficial effects via agonism of CB1 and CB2 receptors in rodent models, these effects and how they translate to human subjects remain unclear.

At low or moderate doses, THC causes an increase in sympathetic activity and inhibition of parasympathetic activity, often leading to tachycardia and increased cardiac output. Acutely, THC use can lead to a 20%-100% rise in heart rate, a slight increase in blood pressure, and up to a 30% increase in cardiac output. The tachycardia response and increased catecholamine concentrations can be proarrhythmic, as well as increase myocardial oxygen demand. THC use also causes an increase in carboxyhemoglobin, which decreases the overall oxygen-carrying capacity, creating a mismatch between increased oxygen demand and decreased delivery to the myocardium.

At higher doses, THC can result in increased parasympathetic activity, leading to hypotension and bradycardia. The hypotension secondary to both parasympathetic activity and activation of CB1 receptors can lead to decreased coronary perfusion pressure, possibly further contributing to myocardial ischemia. Other consequences of THC use include decreased atrioventricular node conduction, reduced left ventricular ejection time, and decreased vascular resistance in skeletal muscle, leading to postural hypotension. Furthermore, the analgesic effects of THC can potentially mask cardiac symptomatology and lead to delays in seeking medical care. Mittelman et al reported that in 3882 individuals with MI, 3.2% reported marijuana use in the 1 year before presentation. In this group, 37 patients smoked marijuana within 24 hours of their MI and 9 had smoked within 1 hour of presentation. The risk of MI was 4.8 times higher in the latter group, and decreased to 1.7 times greater between 1 and 2 hours after use.

Mir et al reported 3 adolescent males who presented with chest pain in the context of smoking both K2 and marijuana. They demonstrated ST segment elevation on ECG, elevated troponin I levels to a maximum of 25 ng/mL, and normal echocardiograms. Two of the 3 patients underwent cardiac catheterization, which revealed normal coronary arteries. McKeever et al reported a patient who presented with substernal pressure after smoking K2 and had evidence of diffuse ST elevation, worse in the inferolateral leads. He had an initial elevation in troponin I that increased during his hospitalization (peak, 8.29 ng/mL). He was treated with a combination of nitroglycerin, morphine, aspirin, Ativan, and Reglan, followed by nitroglycerin infusion and later verapamil because of concerns about coronary vasospasm. Both echocardiogram and cardiac catheterization revealed normal findings, including normal coronary arteries.

Other pediatric case reports have addressed the arrhythmogenic effects of THC. Singh et al reported a 14-year-old male who presented with palpitations, dizziness, and a fall after using marijuana and was ultimately found to have atrial fibrillation necessitating digitalis therapy. After the patient stopped smoking marijuana, he was able to discontinue digitalis therapy and experienced no further recurrence of arrhythmia. Daccarett et al reported a 19-year-old male who presented with syncope after marijuana use who had ST elevation in leads V1-V2 concerning for Brugada pattern without right bundle branch block. Procainamide testing was negative, and echocardiogram was normal. Pratap and Korniyenko reported another 19-year-old male with palpitations and syncope after marijuana use with ST elevation in V1-V2 and incomplete right bundle branch block concerning for Brugada pattern. Troponins and CK-MB were negative, and echocardiogram was normal. Procainamide challenge was negative, and ST changes resolved on repeat ECG.

Our subset of patients had a history of K2 inhalation and evidence of significant ST elevation in a coronary distribution pattern with or without elevated troponin levels. Echocardiogram was normal in all patients who underwent echocardiography, and no patient required cardiac catheterization. Even though these patients did not meet the definition of MI based on ECG changes and elevated troponin levels, they did show evidence of myocardial ischemia.

K2 and other synthetic cannabinoids can potentially cause significant cardiac effects secondary to tachycardia, decreased coronary perfusion, and mismatch of increased oxygen demand and decreased oxygen delivery. Although the reported incidence of MI related to K2 use is extremely low, there may be a higher occurrence of myocardial ischemia that goes unrecognized. The significance of this is unknown, and these patients may require long-term monitoring for the development of wall motion abnormalities and other signs of decreased cardiac function. Furthermore, workups including ECG and troponin levels often are not performed, owing to the absence of specific cardiac complaints. This is further complicated by the decreased regulation of synthetic cannabinoids; there may be additional substances, such as amphetamines, contained within the drug that may increase the risk of cardiac injury, leading to an increased risk of coronary vasospasm. Compliance
with medical care and concern about legal issues may hinder honest reporting during history taking. This may be especially pertinent in adolescents.

Although the ECG abnormalities and increased serum troponin levels were temporally associated with K2 use, we cannot absolutely identify a direct causal relationship in each case. All echocardiograms performed, were normal, but the long-term consequences of K2 use and myocardial ischemia are unknown and require long-term follow-up studies. The lack of specific cardiac symptoms should not deter healthcare providers from obtaining an ECG and possibly cardiac enzyme tests.

Submitted for publication Mar 20, 2015; last revision received May 1, 2015; accepted Jun 2, 2015.

Reprint requests: Bradley C. Clark, MD, Division of Cardiology, Children’s National Health System, 111 Michigan Ave NW, WW 3.0, Washington, DC 20010. E-mail: brclark@childrensnational.org

References

Figure 2. Case 2 ECG on presentation. Normal sinus rhythm, ST segment elevation in the anterolateral leads, and T wave inversions more evident in inferior leads.

Figure 3. Case 3 ECG on A, presentation and B, discharge. A, Sinus tachycardia, possible left atrial enlargement, ST elevation; consider anterolateral injury or acute infarct; ST more elevated in V2-V3. B, Normal sinus rhythm, possible left atrial enlargement, LVH, ST elevation; consider early repolarization, pericarditis, or injury.