Family Medicine and Primary Care: Open Access
Kwag KH, et al. J Family Med Prim Care Open Acc 6: 202.
www.doi.org/10.29011/2688-7460.100202
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Case Report

Cardiovascular Complications of Cannabis: Reports of Prolonged QTc in Adolescents with Cannabinoid Hyperemesis Syndrome

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Citation: Kwag KH, Basouny N, Brown B, Bialik I, Chhabra M (2022) Cardiovascular Complications of Cannabis: Reports of Prolonged QTc in Adolescents with Cannabinoid Hyperemesis Syndrome. J Family Med Prim Care Open Acc 6: 202. DOI: 10.29011/2688-7460.1000202

Received Date: 16 September, 2022; **Accepted Date:** 23 September, 2022; **Published Date:** 27 September, 2022

Abstract

Adolescent use of cannabis has escalated since the drug's legalization in the United States compounded by the social ramifications of the COVID-19 pandemic. Although the neuropsychiatric effects of cannabis have been widely appreciated, its cardiovascular complications are less understood. Here, the authors present two adolescents with Cannabinoid Hyperemesis Syndrome (CHS) who had findings of prolonged corrected QT (QTc) interval in the setting of hypokalemia. In patients with intractable vomiting secondary to cannabis use, multiple factors may increase the interval, including electrolyte abnormalities (hypokalemia), biochemical effects of exogenous cannabinoid itself, or the QT-prolonging properties of antiemetics. Prolonged QTc can precipitate severe arrhythmias, namely torsade de pointes, which can progress to ventricular fibrillation, syncope, and even sudden cardiac arrest. The authors highlight the importance of a screening EKG in CHS patients and discuss alternative antiemetic therapies that do not target the endocannabinoid system.

Keywords: Cannabinoid hyperemesis syndrome; Cannabis; Marijuana; Endocannabinoid System; QT prolongation; QT prolonging drug; Antiemetic; Arrhythmia; Torsades de pointes; Ventricular fibrillation; Nausea and Vomiting; Hypokalemia

Introduction

Cannabis is the most commonly used illicit drug in the United States. Non-medical marijuana is legal for adults in 19 states and the District of Columbia [1]. Widespread availability of the drug has led to a significant rise in adolescent use. A 2018 study reported that an estimated 11.8 million young adults use marijuana in the United States [2]. Additionally, more than one in three high school students (37%) have tried marijuana [2].

Health care institutions across the United States now face the growing problem of cannabis-associated complications. Of particular concern are reports of severe cardiovascular disease, including arrhythmia, myocardial infarction, and even arrest [3-8]. We discuss two adolescents diagnosed with Cannabinoid Hyperemesis Syndrome (CHS) who presented with cardiac symptoms. Both patients demonstrated prolonged QTc and hypokalemia on further work-up.

Patient 1

A 20-year-old female with endometriosis and pelvic inflammatory disease presented to the Emergency Department (ED) with severe nausea, vomiting, epigastric pain, and diarrhea

for two days. Additional history was positive for frequent cannabis use, three to four times per week, and intermittent vomiting for the past two to three months. Haloperidol was administered for nausea and vomiting. The patient requested discharge despite recommendation for admission due to failed oral intake.

The patient returned to the ED that evening due to worsening vomiting with new complaints of chest pain and shortness of breath. Intravenous hydration was initiated. An electrocardiogram for chest pain revealed a prolonged QTc of 477ms (Figure 1a). Troponin was negative. Electrolytes were within normal limits. A second dose of haloperidol was given as the patient was unable to tolerate oral Zofran. On admission, physical exam was remarkable for dehydration, while vital signs exhibited baseline hypertension (maximum 170/190 mm Hg) that persisted throughout her hospital stay. Heart rate remained in the low 60s to 70 beats per minute. Antiemetic medications ondansetron and lorazepam were administered as needed along with famotidine for gastrointestinal prophylaxis. Nifedipine was administered if blood pressures exceeded 140/90 mmHg.

Nausea and vomiting continued despite antiemetic therapy. The patient further reported relief of symptoms with hot showers leading to the diagnosis of CHS. On hospital day one, the patient had an episode of syncope. After regain of consciousness, increased nausea was reported. An additional dose of haloperidol was given.

During hospital day two, the patient experienced recurrent chest pain. An echocardiogram showed normal anatomy with adequate ventricular function. Repeat EKG showed prominent U waves and persistently prolonged QTc, now at 489 ms. Electrolytes were significant for hypokalemia (2.7 mmol/L). Potassium repletion was initiated.

On hospital day three, potassium normalized from 2.7 mmol/L to 3.5 mmol/L; however, QTc remained prolonged to 472 ms with continued U waves. The patient improved throughout her hospital stay. The patient did not follow up with outpatient cardiology. However, a subsequent ED visit, also for intractable vomiting, showed persistence of hypertension and U waves on EKG.

Patient 2

An 18-year-old female with a past medical history of Premature Ventricular Contractions (PVC), Premature Atrial Contractions (PAC), and persistent tachycardia presented to the ED with vomiting after consumption of cannabis-containing brownies, with associated left ear tinnitus, tachycardia, and lightheadedness. Intravenous fluids were initiated along with ondansetron and Maalox. An EKG for evaluation of tachycardia (maximum 147 beats/minute) was significant for a prolonged QTc of 566ms (Figure 1b). Troponin and a thyroid panel were unremarkable. Electrolytes were significant for mild hypokalemia (3.3 mmol/L) and urine was positive for cannabinoids.

The patient was given one dose of adenosine for tachycardia. Heart rate remained elevated despite therapy, and the patient was admitted to the pediatric intensive care unit. Potassium was repleted. Repeat EKG showed normalization of QTc to 413 ms and correction of potassium level to 4.3 mmol/L. Echocardiogram showed trivial mitral regurgitation with good left ventricular function. Tachycardia resolved on hospital day two (79-89 beats/minute) and the patient was discharged. During subsequent outpatient cardiology visits, the patient continued to complain of retrosternal chest pain, most likely functional with a normal cardiac work-up and history of anxiety. At her most recent follow-up, the patient reported resolution of chest pain.

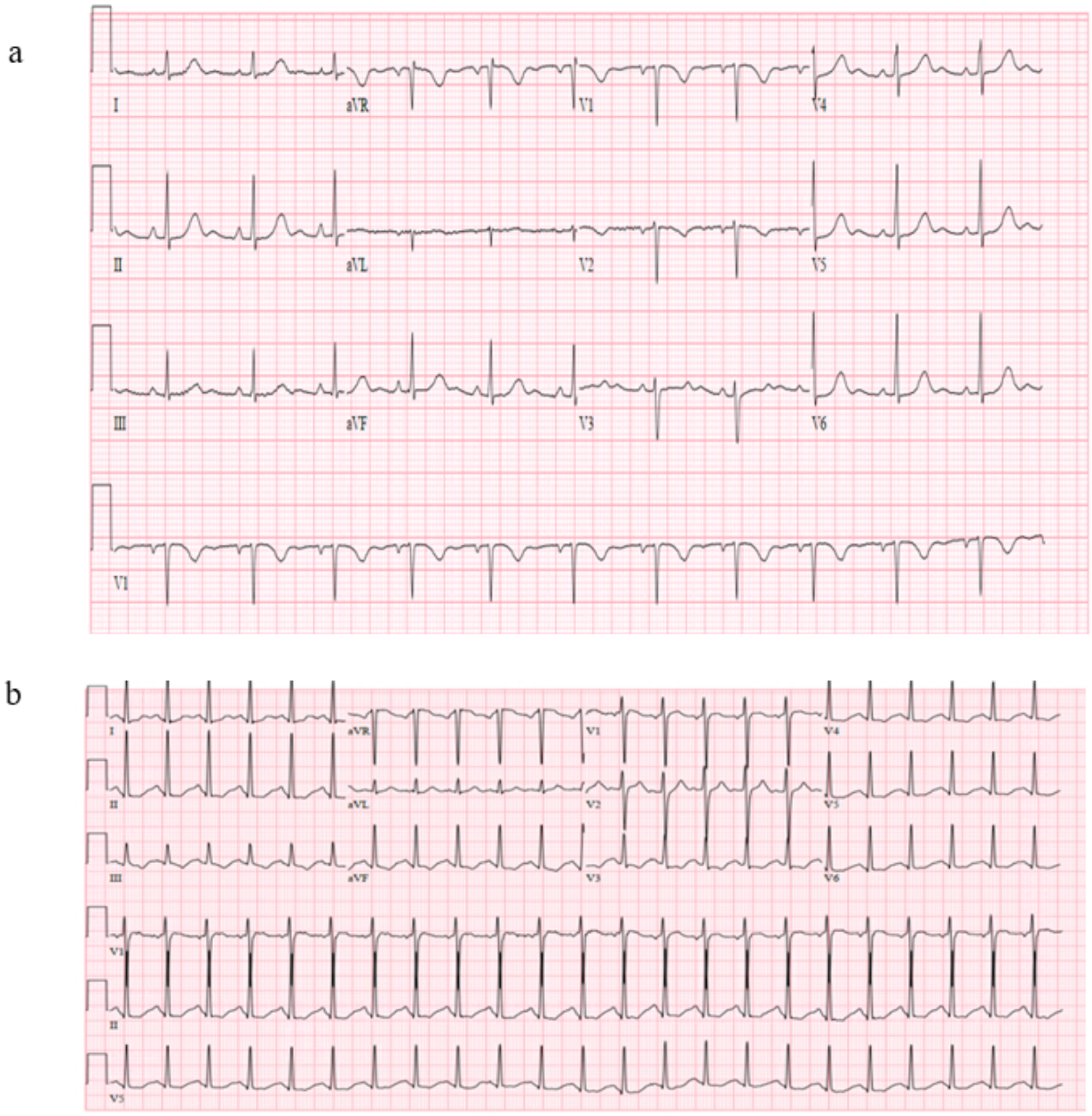

Figure 1: EKG showing a) prolonged QTc of 477ms in Patient 1, b) prolonged QTc of 566ms in Patient 2.

Discussion

In this case report, we discuss two adolescent females with intractable vomiting secondary to Cannabinoid Hyperemesis Syndrome complicated by cardiac presentations of tachycardia (patient 1) and chest pain (patient 2) along with hypokalemia and prolonged QTc interval. Only one publication to date highlights a pediatric patient who demonstrated prolonged QTc in the setting of frequent cannabis wax vaping that exacerbated to Torsade de pointes and cardiac arrest [7]; this patient had a genetic predisposition to QTc prolongation. A 22-year-old female with CHS and vomiting-induced hypokalemia developed Torsade de pointes that deteriorated to cardiac arrest and death; mutation of cardiac genes MYBPC3 and RYR2 genes were identified [9].

Paradoxically, cannabis can exert both anti- and pro-emetic properties. The pro-emetic effect of cannabis is better understood and therapeutically utilized such as in chemotherapy-induced nausea. Research on the Endocannabinoid System (ECS) and the role of CNS and gut-specific cannabinoid receptors CB1 and TRPV1 sheds light on the dual phenomenon. Nausea and vomiting are mediated by the Hypothalamic-Pituitary-Adrenal (HPA) axis, vagus nerve, and brain stem [4]. The ECS provides negative feedback inhibition on the HPA axis. This inhibition is thought to be mediated through the G-protein-coupled cannabinoid receptor CB1, accounting for the antiemetic effect of cannabis. The pro-emetic effect of cannabis may be explained by the Transient Receptor Potential Vanilloid 1 (TRPV1) located in the gastrointestinal tract and CNS. Highly expressed in the area postrema, TRPV1 exert strong antiemetic effects when activated by agonists endocannabinoids and exogenous cannabinoids [10,11]. Repeated stimulation of TRPV1 during chronic cannabinoid exposure, however, is hypothesized to desensitize TRPV1 via receptor phosphorylation; another hypothesis suggests the downregulation of TRVP1 ligands with repeated exposure [10]. Food deprivation and stress, which often accompany chronic cannabis use, stimulate ACTH-mediated lipolysis. As (9)-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, is stored in adipocytes, the result is an increased concentration of the molecule and pro-emetic exertion [14].

The clinical presentation of CHS involves nausea and intense, multiple episodes of vomiting with characteristic relief from symptoms by hot showers. Diagnosis of CHS depends on the duration and chronological pattern of symptoms according to the Rome IV criteria [14]. Such intractable vomiting can lead to dehydration and electrolyte abnormalities include hypocalcemia, hypomagnesemia, and particularly, hypokalemia. A single-center prospective observational study at a tertiary care hospital cited hypokalemia as the most frequent electrolyte abnormality detected in patients with prolonged QTc [15].

Hypokalemia is defined as a potassium level less than 3.5 mmol/L. EKG changes (e.g., increased QT interval and a prominent U wave with a small T wave) occur with levels below 2.7mmol/L [16]. Even modest hypokalemia ranging from 2.8 towards 3.5 mmol/L has been associated with a prolonged QTc up to 660 ms [17]. If QTc exceeds 500 ms, patients have a two- to three-fold increase in risk for Torsades de Pointes (TdP) [18]. QTc normalized with potassium repletion in Patient 2. In Patient 1, however, correction for hypokalemia did not resolve QTc prolongation, providing evidence for additional mechanisms of this EKG finding.

Cannabis may directly increase QTc through the delayed rectifier potassium channel (IKr) and parasympathetic system. IKr plays an important role in cardiac repolarization, the inhibition of which elevates QTc [19]. Bradycardia from parasympathetic activation is also associated with increased QTc [19,20]. Prolonged QTc predisposes to TdP, which can deteriorate to ventricular fibrillation [7,8]. Additional arrhythmias have been reported with cannabis use such as atrial fibrillation, especially in young patients without additional risk factors [7,8], and Brugada syndrome [21].

In addition to arrhythmias, cannabis exerts a range of cardiac manifestations and complications. Hypertension and tachycardia were observed in our patients. Located in the heart and vascular smooth muscle, CB1 receptors mediate both the sympathetic and parasympathetic effects of cannabis. Elevated heart rate, enhanced sympathetic tone, and increased catecholamine levels have been demonstrated at lower doses, while bradycardia and hypotension have been observed at high doses [2]. Increased myocardial oxygen demand due to tachycardia paired with decreased oxygen supply as a result of high carboxyhemoglobin levels can lead to myocardial ischemia [2]. The procoagulant effect of cannabis on platelet CB1 and CB2 receptors and consequent thrombus formation can cause myocardial infarction [2]. Chronic use can increase the risk of angina through diminished autonomic nervous system signal transduction, increased serum aldosterone, vasoconstriction, and hypertension [6].

Vomiting and nausea in CHS are often refractory to first-line antiemetics such as ondansetron and metoclopramide. These medications have been shown to prolong the QTc on EKG. More potent therapies such as haloperidol with stronger QT-prolonging potentials are consequently administered, further increasing the risk for cardiac arrhythmias. Similar to the mechanism of cannabinoids, antiemetics affect QT interval via IKr [22]. Haloperidol more specifically blocks IKr and can prolong QT by 15-30 ms in a dose-dependent manner [23]. Both patients received multiple doses of haloperidol (2 mg per dose) for nausea and vomiting during their hospitalization.

Although most episodes of antiemetic-associated prolonged QTc are clinically silent and self-limited, these episodes can be significant in patients with additional risk factors for cardiac arrhythmias such as congenital long QT syndrome. Accordingly, antiemetics that do not target ECS should be considered in CHS patients. Benzodiazepines (administered in Patient 1), which enhance the inhibitory action of γ-aminobutyric acid type A (GABA) receptors, may serve as an effective alternative, although the possible effects of bradycardia and hypotension should be considered [24]. Scopolamine, which can be applied as a transdermal patch, relieves nausea and vomiting by competitively inhibiting muscarinic receptors [25]. Fosaprepitant is a Neurokinin-1 Receptor Antagonist (NK1RA) commonly used to prevent chemotherapy-induced vomiting. A study of four randomized controlled trials examining the safety of three different antiemetic regimens containing NK1RA found the drug to be safe with very few adverse cardiac effects [25]. Dexamethasone acts on the glucocorticoid receptor and is indicated for post-operative nausea and vomiting [26]. These medications have not been linked with QT prolongation. Although recommended in adults, their efficacy and safety have not been studied specifically in pediatric patients with CHS.

Conclusion

Patients with Cannabinoid Hyperemesis Syndrome impose a significant burden on the health care system, often requiring extensive inpatient work-up to exclude acute life-threatening disease. Severe cannabis-associated cardiac complications such as arrhythmias may be prevented through a screening EKG for QTc prolongation and evaluation of electrolytes. A careful history is important to identify additional risk factors for arrythmias such as a family history of long QT, congenital long QT syndrome, and thyroid disease. Clinicians should be mindful when selecting antiemetics given the QT-prolonging effect of many first-line therapies. With the expected rise in cannabis use in the United States with its legalization, it is imperative for health care professionals to discuss with patients the cardiovascular complications of cannabis and offer support for drug cessation.

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