Disseminated Intravascular Coagulopathy Secondary to Unintentional Brodifacoum Poisoning via Synthetic Marijuana

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Abstract
Recent evidence demonstrates a rising epidemic of unintentional brodifacoum poisoning associated with synthetic cannabinoid use. Synthetic cannabinoid use is on the rise because of its inexpensiveness as well as difficulty to screen and regulate. We present a rare case of severe coagulopathy and cardiac arrest secondary to synthetic cannabinoid use complicated by brodifacoum toxicity.

Keywords: Disseminated intravascular coagulopathy; Synthetic marijuana; Brodifacoum poisoning

Introduction
Synthetic cannabinoids (SCs) are inexpensive and have quickly spread worldwide since introduction in the early 21st century. The multiple analogs of SCs render urine drug testing difficult [1] and routine urine toxicology ineffective [2]. This subsequent explosion in SC use has coincided with an alarming increase in complications including myocardial infarction [2-6], cerebrovascular disease [7, 8], psychosis [9], seizures [10], acute kidney failure [11-14], and death [3, 15]. We present a rare case of severe coagulopathy and cardiac arrest secondary to SC and unintentional brodifacoum exposure.

Case Report
A 38-year-old man with previous diagnoses of bipolar disorder, post-traumatic stress disorder and polysubstance abuse presented with a 3-day history of epistaxis, hematuria, rectal bleeding, bruising and diffuse abdominal pain. His medical history was positive for daily marijuana as well as synthetic marijuana use and was otherwise negative. Vital signs were normal. His physical exam was significant for ecchymosis of the abdomen and extremities.

Initial workup was remarkable for elevated prothrombin time (PT) at > 154 s (normal range (NR): 9.2 - 11.8 s) and activated partial thromboplastin time (aPTT) at > 169 s (NR: 23 - 30 s), as well as an undetectably high international normalized ratio (INR) (NR: 0.9 - 1.1 s). D-dimer was reported to be > 35 mg/L (NR: 0.19 - 0.9 mg/L), lactate dehydrogenase (LDH) was elevated at 582 Unit/L (NR: 84 - 246 Unit/L) and low fibrinogen was 64 mg/dL (214 - 407 mg/dL) without schistocytes on peripheral blood smear. Liver function tests were within normal limits. His complete blood count showed white blood cell count (WBC) of 9,870/mm³, hemoglobin of 15.9 g/dL, hematocrit of 47.2%, and platelets of 287,000/mm³. Urine toxicology was positive for both cannabinoids and opioids, and urinalysis was consistent with hematuria.

The patient was diagnosed with disseminated intravascular coagulopathy (DIC). Initial resuscitative efforts included intravenous fluids, fresh frozen plasma, cryoprecipitate, vitamin K₁, and factor IX concentrate. The patient was found hours later outside his hospital room unconscious and in pulseless electrical activity (PEA) arrest. The patient did have return of spontaneous circulation but the etiology of his cardiac arrest remained unknown. Maryland Poison Control was contacted, who were concerned for potential brodifacoum-laced synthetic cannabinoid use. Over the course of his hospital stay, he required immense doses of vitamin K₁ in oral and intravenous doses. His INR trends and treatment measures are depicted in Figure 1.

The patient was successfully discharged on daily oral vitamin K with a discharge INR of 1.1. Unfortunately, the patient was noncompliant with his medication and presented 3 days after discharge to the emergency department with new onset left upper extremity deep vein thrombosis and an INR of 7.2. He was given intravenous vitamin K in the emergency department but left against medical advice and was lost to follow up.

Discussion
SC toxicity is on the rise in the United States of America...
SCs come in many varieties, and clinicians should be aware of the current monikers including “Spice”, “K2”, “Cloud 9” among many others [17]. Common symptoms of SC exposure consist of agitation, depression, psychosis and coma [16] as well as tachycardia, hypertension, chest pain, hallucinations and vertigo [17]. A recent case series demonstrated that out of 456 patients treated for SC intoxication, 277 reported SC as the sole toxic agent. Among these cases, >25% occurred in the pediatric population between ages 13 and 18 years old, and 83.1% of patients were male [16]. Caviness et al reported that SC use often coincides with binge drinking and recreational drug use including marijuana [18]. No antidotes to the effects of SCs currently exist [16].

From March to July of 2018, the Illinois Department of Health reported 255 patients with SC-associated coagulopathy, and eight mortalities [19]. Kelkar and colleagues identified 34 patients with SC-associated coagulopathy with a mean age of 37 years old, and presenting symptoms of gross hematuria and abdominal pain. Mean INR on presentation was 15.8. Vitamin K1 (phytonadione) was given orally to all patients and 68% of cases were supplemented with intravenous vitamin K1, 55% with fresh frozen plasma, and one case with 4-factor prothrombin complex concentrate. Eight patients left against medical advice and six were subsequently readmitted. Serum samples from these patients tested positive for brodifacoum [20]. As of January 1, 2019, the Maryland Poison Center at the University of Maryland School of Pharmacy reported notification of 44 cases with exposure to SC with significant elevations in INR and hemorrhage with 9% mortality [21].

In the USA, synthetic cannabis production remains illegal in federal law, and therefore federally unregulated [22]. At this time, it is unknown how brodifacoum was incorporated into the patient’s SC; however, in cannabis production facilities, brodifacoum is often applied to the base of Cannabaceae stalks as a rodenticide. Quantities up to 25 kg can be found at these facilities, and have been correlated to an increased death toll on local animals [23]. Compared to warfarin, the strong hydrophobicity in brodifacoum allows for longer tissue retention, a half-life lasting from 20 days to 12 months, and a potency 100 times stronger than warfarin in reducing vitamin K-dependent coagulation factors [24]. Toxicity in rat models was higher when inhaled than ingested [25]. Unfortunately, diagnosis remains difficult. A recent study by Ng et al stated that in 41 identified cases of extended release warfarin toxicity, 25% of patients did not have obvious exposure history, nor could identify the causative agent. Occult poisoning was frequently missed on initial clinician visit, leading to delayed initiation of treatment [26].

The Saint Frances Medical Center in Illinois has developed a criterion to diagnose SC-associated coagulopathy. Major criteria include: 1) presence of vitamin K-dependent factor coagulopathy (defined as a prothrombin time ≥ 14.8 s and an INR ≥ 1.3); and 2) recent exposure to SCs (within the past 30 days). The minor criteria include: 1) active bleeding symptoms; 2) exposure to contaminated SCs obtained from a person with known superwarfarin poisoning; and 3) positive toxicology for superwarfarin. The use of prescribed anticoagulants was listed as a confounding factor. Patients with both major criteria and at least one minor criterion were diagnosed with SC-associated coagulopathy. In cases of concurrent anticoagulant use, an anticoagulant poisoning panel, which detects warfarin, dicumarol, diphenacoum, chlorophacinone, difenacoum, brodifacoum, and bromadiolone, was utilized [20].

Treatment of brodifacoum toxicity depends greatly on the method of poisoning [27]. Studies in a canine animal model have demonstrated that if emesis is induced within 1 h of ingesting brodifacoum rodenticide, 10-77% of brodifacoum is expelled with the gastric contents. In this canine population, all the animals did well without further medical treatment and
Author Contributions

AC, MA, JK and AM equally contributed in the writing of the paper. All authors edited and approved the final manuscript.

Abbreviations

aPTT: activated partial thromboplastin time; BT: blood transfusion; DIC: disseminated intravascular coagulopathy; HD: hospital day; INR: international normalized ratio; IV: intravenous; LDH: lactate dehydrogenase; NR: normal range; PEA: pulseless electrical activity; PO: oral; PT: prothrombin time; SC: synthetic cannabinoid; WBC: white blood cell count; USA: United States of America

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