Severe Coagulopathy Associated with Synthetic Cannabinoid Use: A Case Report

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Abstract

Background: The Center for Disease Control and Prevention has declared a national health advisory due to the emerging association of brodifacoum with numerous case reports of life-threatening coagulopathy in synthetic cannabinoid users since March 2018. The link between synthetic cannabinoids and brodifacoum remains unclear.

Methods: This case report describes the presentation, workup, and treatment of an individual who experienced severe hemorrhage due to brodifacoum poisoning secondary to synthetic cannabinoid use. We obtained permission to use his medical records for this report.

Results: The male patient was found to have a deficiency in vitamin K-dependent clotting factors and fifteen times the reporting limit of brodifacoum in his blood. He was started on high-dose vitamin K therapy, which gradually resolved his hemorrhage and improved his coagulation profile. He may require high-dose vitamin K for up to six months.

Limitations: In North Carolina, serum testing for brodifacoum is performed at a designated poison center and can take up to four weeks to result. This creates a delay in confirming the diagnosis.

Conclusion: Clinicians should suspect brodifacoum poisoning in synthetic cannabinoid users that present with bleeding and coagulopathy. This case serves to emphasize the importance of seeking a thorough social history in patients and promptly obtaining coagulation profiles to initiate high-dose vitamin K therapy, if indicated, and treat brodifacoum poisoning.

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Introduction

Adverse effects of synthetic cannabinoids have been reported globally and in every U.S. state. These compounds are created in laboratories, targeting cannabinoid receptors to produce a "high" similar to that which users experience from marijuana. Unfortunately, these compounds are commonly linked to neurologic, cardiac, gastrointestinal, and psychiatric effects.[1] Since early 2018, synthetic cannabinoids have been linked to life-threating hemorrhage by way of a compound called brodifacoum. Brodifacoum is a highly lipophilic agent that became commercially available in 1975 as a novel poison against warfarin-resistant rodents. It is known as a "super-

warfarin" drug due to its longer half-life and greater potency than warfarin. The primary mechanism of action is by inhibiting vitamin K epoxide reductase, an enzyme required to reduce vitamin K to its active form. Several case reports as early as 1993 have linked toxic brodifacoum ingestion with hemorrhage and coagulopathy in humans.[2] Diagnoses have been confirmed by detecting elevated serum brodifacoum levels and high-dose vitamin K replacement has been the primary therapy.

Case Report

Our patient is a 57-year-old male with a past medical history of hypertension, chronic hepatitis C, and prior alcohol abuse who presented to the emergency department with gross hematuria. He reported one day of progressively worsening hematuria without associated dysuria, incontinence, fevers, or chills. He also reported having mild, intermittent, left-sided flank pain for the last three months, which was progressively worsening over the last few days. He denied recent alcohol or tobacco use.

The patient was afebrile, normotensive, had a pulse of 88 beats per minute, and a respiratory rate of 18 breaths per minute. On physical exam, he appeared well, had no ecchymoses or petechiae on the skin, and his abdominal exam was benign. He had mild left-sided costovertebral angle tenderness, but no other abnormalities. Genitourinary exam was normal and digital rectal exam revealed a small, firm prostate with no nodularity or tenderness.

Investigations

Workup in the emergency department consisted of a complete blood count (CBC) that showed a mild leukocytosis to 10,800 cells/μL, with absolute neutrophil count of 8,500 cells/μL, platelet count of 201,000 cells/μL, and hemoglobin of 13.0 g/dL. Basic metabolic panel showed a sodium of 131 mmol/L, BUN of 36 mg/dL, and creatinine of 3.09 mg/dL (baseline 1.0 mg/dL). Urinalysis was positive for nitrites, leukocyte esterase, large blood, glucose, ketones, and protein. Computerized tomographic (CT) scan of his abdomen/pelvis without contrast demonstrated bilateral hydronephrosis, as well as bilateral renal enlargement and likely parenchymal edema. There was extensive perinephric stranding of the ureters. Two 3mm calcifications were identified over the expected course of the bilateral ureters, which were not present on a prior exam from March 2015, but were deemed unlikely to account for the degree of hydronephrosis.

Treatment

The patient was given 1g of ceftriaxone intravenously (IV), one liter of normal saline IV, and subsequently admitted to the family medicine service, where urology was consulted. Urology placed bilateral ureteral stents and noted that the patient's efflux of dark red urine before and after stenting seemed to suggest alternate pathology, perhaps glomerular, as it seemed out-of-proportion to that typically seen with ureteral stones. Retrograde pyelogram confirmed that the patient's hydronephrosis was insignificant.

The next morning, he developed oral bleeding that was believed to be from trauma secondary to intubation during the ureteral stenting procedure. Otolaryngology (ENT) was consulted, where a transnasal fiberoptic laryngoscopy (TNFL) was performed and showed an actively bleeding right buccal ulceration and vocal fold ecchymosis. The patient was placed on strict voice rest and was transferred to the intensive care unit for airway protection. A coagulation panel showed prothrombin time (PT) >100 seconds, partial thromboplastin time (PTT) >122 seconds, and international normalized ratio (INR) too high to calculate. Repeat CBCs over the day showed a drop in the patient's hemoglobin from 13.0 to 9.8, then 7.1, and he required transfusion of 2 units of packed red blood cells. The patient's platelets remained within normal limits. Extrinsic and intrinsic factor panels showed significant reductions in factors II, VII, IX, and X, suggesting a vitamin K deficiency or antagonistic process.

Hematology/Oncology was consulted and recommended supplementing vitamin K and transfusing fresh plasma. Over a one week period, vitamin K was started at 5mg orally daily, but given persistent elevations in his PT/PTT/INR, the dose was titrated up to 25mg every six hours until his coagulation studies normalized. His coagulation studies did not normalize until the larger dosing of vitamin K was administered. For reference, an adult dietary supplement dose of vitamin K is 5-10mg per day. Hemoglobin levels stabilized once frozen plasma and high-dose vitamin K therapy were initiated, and his urine gradually began to clear.

As his condition stabilized, the patient was transferred back to the family medicine service. Late during this admission, the patient ultimately admitted to a history of smoking K2, a synthetic cannabinoid, approximately one month prior to his admission. A serum brodifacoum level of 155ng/mL was measured, which was elevated compared to the reporting limit (10ng/mL).

Differential Diagnosis

In addition to brodifacoum poisoning, the etiology of the coagulopathy in this case, the following should be considered based upon this patient's presentation with gross hematuria: nephrolithiasis, coagulopathy secondary to liver pathology (cirrhosis, hepatitis C, etc.), intrinsic glomerular disease, vitamin K deficiency or antagonism, platelet dysfunction, renal cell carcinoma or other malignant renal mass, disseminated intravascular coagulopathy (DIC), and hemophilia.

Discussion

The patient presented with gross hematuria and subsequently developed laryngeal hemorrhage with no prior or familial history of hemophilia or coagulopathy. Ureteral stones were cleared by stenting, and neoplastic processes were ruled out by imaging. Glomerulonephritis was ruled out as the patient remained normotensive, had normal urine production, and had a normalization of his creatinine within 48 hours. With our patient's elevated PT, PTT, and INR in the setting of a normal platelet count and elevated fibrinogen, DIC was unlikely. The patient had normal liver function tests and prior CT showed no evidence of cirrhosis, making a coagulopathy associated with liver disease from chronic hepatitis C unlikely.

The significantly low levels of factors II, VII, IX, and X from the patient's extrinsic and intrinsic factor panels confirmed a vitamin K deficiency or antagonistic process, which led to treatment with high-dose vitamin K. The diagnosis of acute brodifacoum poisoning was confirmed when serum levels returned significantly elevated. The high doses of vitamin K were required to overcome the inhibition of vitamin K reductase and vitamin K epoxide reductase by brodifacoum, as shown in **Figure 1**.

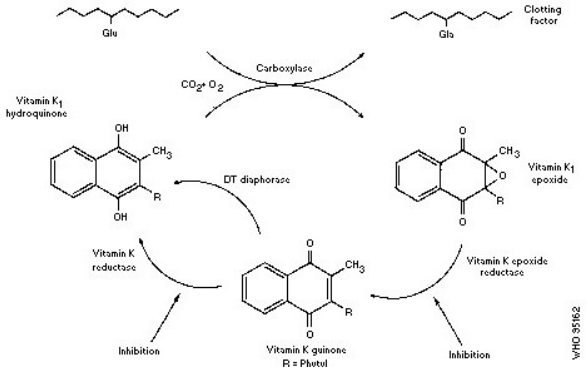

Figure 1. Inhibition of vitamin K reductase and epoxide reductase by warfarin.[3] *Reprinted with permission.*

Synthetic cannabinoid use has significantly increased in the past decade. Regulation has been difficult due to the numerous synthetic varieties, making classification of the compounds difficult. Formulations colloquially known as "K2" or "Spice," which often do not correspond to a single cannabinoid, commonly sell at convenience stores and paraphernalia shops, despite federal regulatory efforts.[4] Currently, marijuana and many identified synthetic cannabinoids are classified as Schedule I Controlled Substances, along with heroin and other opioids. However, the numerous varieties of cannabinoids and ease by which to create new cannabinoids in the laboratory make for difficult regulation.

Several case reports have identified an association with brodifacoum and synthetic cannabinoids, but a causality has not been proven. K2 and Spice are produced by spraying synthetic cannabinoids, often created in a laboratory, over non-psychoactive plants, with the drug effects attained by smoking and inhaling the mixture by pipe or cigarettes. The authors of this case report speculate that brodifacoum is used as an additive to prolong the effects of the cannabinoids, though this link remains unclear. As of July 13, 2018, over 250 cases of brodifacoum poisoning by synthetic cannabinoid use have been reported to the CDC, and its incidence is increasing.[5] Similar cases have been reported in Illinois (n=164), Maryland (n=20), and other states.[6] This marks the fourth documented case in North Carolina (Michael C. Beuhler, MD, email communication, September 2018).

Conclusion

Our patient eventually was titrated to a high-dose vitamin K regimen at 25mg orally twice daily and was discharged from the hospital. This is a costly medication: ten 5mg tablets cost approximately $223 in the United States—the dose the patient was receiving daily. He received regular PT/PTT/INR checks, which stabilized in the normal range after one month, but he required high-dose vitamin K for six months. The patient's brodifacoum level dropped significantly after one month of treatment from 155ng/mL to 50ng/mL. Two months later, it further decreased to 18ng/mL, but it remained at this level for another two months before then becoming undetectable. As with our patient, treatment courses of high-dose vitamin K may continue for approximately six months or until the patient has two consecutive brodifacoum levels under 10ng/mL.[7] This illustrates the toxin's lipophilicity.

This case highlights the importance of asking detailed social (i.e. illicit substance use) histories, specifically asking about synthetic cannabinoid use, in patients presenting with unexplained significant bleeding. It is also important to consider vitamin K-dependent antagonist coagulopathy (e.g., brodifacoum poisoning) after reported synthetic cannabinoid use within the last three months.

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Disclosures

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