The Journal of Emergency Medicine, Vol. 57, No. 1, pp. 47–50, 2019

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2019.03.007

Selected Topics: Toxicology

HEMORRHAGIC SOFT TISSUE UPPER AIRWAY OBSTRUCTION FROM BRODIFACOUM-CONTAMINATED SYNTHETIC CANNABINOID

Christopher H. Ross, MD, FRCPC,* Parvinder Singh, MBA,† and Erin L. Simon, DO†‡

*Department of Emergency Medicine, Mercyhealth Wisconsin and Illinois, Rockford Memorial Hospital, Rockford, Illinois, †Department of Emergency Medicine, Cleveland Clinic Akron General, Akron, Ohio, and ‡Associate Professor, Northeastern Ohio Medical University, Rootstown, Ohio

Corresponding Address: Erin L. Simon, DO, Department of Emergency Medicine, Cleveland Clinic Akron General, 1 Akron General Avenue, Akron, OH 44307

☐ **Abstract—Background: More than 60 types of cannabinoids are found in nature; the remaining are chemically synthesized analogs of natural cannabinoids. Synthetic cannabinoids were first reported in the United States in 2008. These compounds are usually smoked by users and are sold under various names. Synthesized products have clinical effects that are similar to the effects of cannabis, which include tachycardia, conjunctival injection, nystagmus, vomiting, and ataxia. In cases of acute overdose, hyperthermia, acute kidney injury, seizures, and rhabdomyolysis can occur. Case Report: Deaths and life-threatening coagulopathies caused by brodifacoum (BDF) adulteration of synthetic cannabinoids have been reported in Illinois and other regions of the United States. BDF is a long-acting vitamin K–dependent antagonist that is often used as rat poison and that can cause massive hemorrhage. BDF is sometimes referred to as "superwarfarin" because the anticoagulant effect is 100 times greater than warfarin on a molar basis and its half-life is 20–130 days, which markedly exceeds that of warfarin. The rationale for lacing synthetic cannabinoids with BDF may be associated with attempts to enhance psychoactive effect of the drug, keeping the user high for a longer period of time because of lipid storage, hepatic metabolism, and slow release. We present the case of a healthy 27-year-old man who developed severe soft tissue hemorrhage and airway obstruction after use of a cannabinoid laced with BDF. Why Should an Emergency Physician Be Aware of This?: To date there have been no case reports documenting severe soft tissue hemorrhage leading to airway obstruction and respiratory failure from synthetic cannabinoid use, whether or not the synthetic cannabinoid has been adulterated. Severe complications can arise from use, and treatment includes vitamin K and supportive therapy because the resulting coagulopathy can take days to weeks to resolve.** © **2019 Elsevier Inc. All rights reserved.**

☐ **Keywords—brodifacoum; cannabinoid; synthetic marijuana; soft tissue hemorrhage; coagulopathy**

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INTRODUCTION

Synthetic cannabinoids are a class of drugs that have grown in popularity throughout the United States and Europe over the past decade. More than 60 types of cannabinoids are found in nature; the remaining are chemically synthesized analogs of natural cannabinoids. Synthetic cannabinoids were first reported in the United States in 2008, and synthetic cannabinoids have caused intoxication requiring emergency department visits in significant numbers (1). These compounds are usually smoked by users and are sold under various names, including "K2," "Spice," "Crazy Monkey," "Kush,"

RECEIVED: 18 November 2018; FINAL SUBMISSION RECEIVED: 27 January 2019;
ACCEPTED: 4 March 2019

"Kronic," and "Chill X" (1,2). Synthetic cannabinoids are often marketed as a safe legal alternative to cannabinoid. However, they are not safe and may affect the brain much more powerfully than cannabinoid. Their effects can be unpredictable and, in some cases, more dangerous or even life-threatening. In the spring of 2018, bleeding suddenly emerged as a new consideration in patients using synthetic cannabinoid in the Midwest, and this complication soon expanded to the East Coast. Synthesized products have clinical effects that are similar to those of cannabis, including tachycardia, conjunctival injection, nystagmus, vomiting, and ataxia (2,3). In cases of acute overdose, hyperthermia, acute kidney injury, seizures, and rhabdomyolysis can occur.

Deaths and life-threatening coagulopathies caused by brodifacoum (BDF) adulteration of synthetic cannabinoids have been reported in Illinois and other regions of the United States. BDF is a long-acting vitamin K–dependent antagonist that is often used as rat poison and that can cause massive hemorrhage (4). BDF works by blocking quinone reductase and epoxide reductase to prevent the conversion of vitamin K epoxide to vitamin K hydroquinone (K1), which is required for the synthesis of activated factors II, VII, IX, and X and factors C, S, and Z. BDF is sometimes referred to as "superwarfarin" because the anticoagulant effect is 100 times greater than warfarin on a molar basis and its half-life is 20–130 days, which markedly exceeds that of warfarin (3). The rationale for lacing synthetic cannabinoids with BDF may be associated with attempts to enhance the psychoactive effect of the drug, keeping the user high for a longer period of time because of lipid storage, hepatic metabolism, and slow release (3,5,6). Compared with warfarin, BDF features greater affinity for K1-2,3-epoxide reductase, disrupts the K1-epoxide cycle at multiple points, and causes hepatic accumulation and profoundly longer biological half-lives because of prolonged lipid solubility and enterohepatic circulation (6,7).

The elimination half-life of brodifacoum has been reported to range from 16–36 days, with case reports of up to 270 days in intentional chronic exposures (8,9). Treatment with vitamin K1 provides active cofactor, bypassing the inhibited enzymes. However, considering the lack of regeneration of spent cofactor to vitamin K1, poor oral absorption of vitamin K1, and the long elimination half-life of many superwarfarins, patients require regular large doses of vitamin K1 for a prolonged course to continue producing clotting factors.

CASE REPORT

A 27-year-old man presented to the emergency department (ED) with complaints of a 1-day history of a sore throat. He was subsequently triaged to the ED "fast track." The patient denied fevers, chills, or other complaints. He reported being seen at an outside ED the day before for hematuria and was diagnosed with "probable kidney stones," but a computed tomography scan was negative for ureterolithiasis. The patient did not report a history of coagulopathy or bleeding disorder; however, on social history he admitted to smoking the synthetic cannabinoid K2 1 month before presenting to the ED.

On presentation to the ED he was tachycardic, mildly tachypneic, and he reported feeling some shortness of breath but was speaking complete sentences and had no changes in phonation. His vital signs were a heart rate of 110 beats/min, respiration 22 breaths/min, blood pressure 162/106 mm Hg, temperature 97.4°F, and oxygen saturation of 100% on room air. An examination of his oropharynx revealed subungual bruising with elevation of his tongue upward and backward from the floor of the mouth. An examination of his neck revealed a "brawny" neck with thickened skin and with what appeared to be bruising. An examination of his chest revealed no stridor and good breath sounds bilaterally. Because of concern for airway patency, nasopharyngoscopy was performed by the emergency physician, which revealed severe soft tissue swelling of the posterior pharynx and supraglottic region. An ear, nose, and throat specialist and an anesthesiologist were consulted to assist in definitive airway control. The ear, nose, and throat specialist suggested that a computed tomography scan of the neck be performed to better identify anatomy of the neck because of significant neck swelling in the event that a surgical airway was required. A computed tomography scan of the neck found marked soft tissue swelling in prevertebral soft tissue, the epiglottis, the tongue, and the floor of the mouth (Figure 1). The swelling involved the submandibular region with resultant airway stenosis that was greatest at the level of epiglottis (Figure 2). An international normalized ratio in the ED was reported back as immeasurably prolonged, and his partial thromboplastin time was >100, indicating severe coagulopathy. A toxicologist was consulted and the patient was given intravenous vitamin K and fresh frozen plasma. The patient was also given intravenous diphenhydramine 50 mg, intravenous dexamethasone 20 mg, and 1 dose of intramuscular epinephrine 0.3 mg before leaving the ED for operating room intubation. In the operating room, nasotracheal intubation via fiberoptic scope required several attempts for definitive airway control. The patient was subsequently taken to an intensive care unit (ICU) for continued management.

The patient remained intubated and sedated in the ICU. Poison control service continued to assist in management and recommended intravenous vitamin

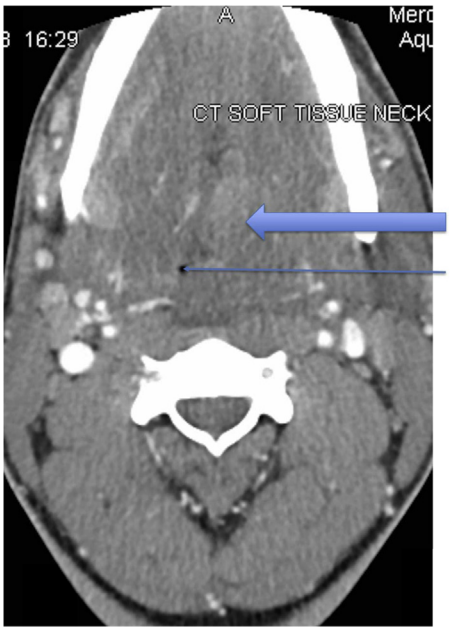

Figure 1. Posterior pharyngeal region showing significant soft tissue swelling and severe airway narrowing. The narrow arrow shows extreme narrowing of the airway and the thick arrow shows extensive edema of the tongue and muscle groups of the mouth.

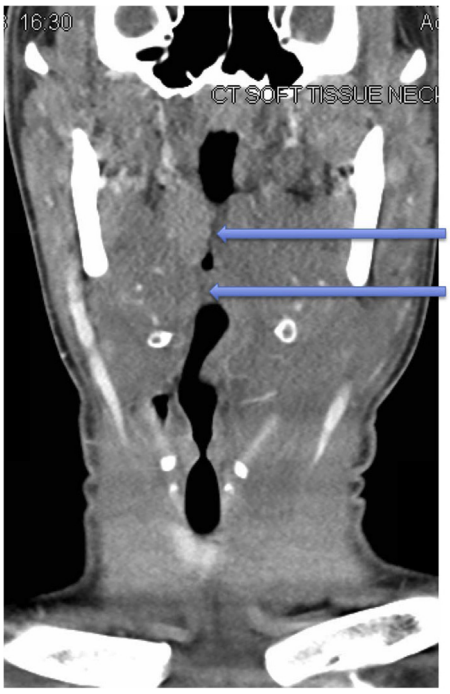

Figure 2. Coronal cut through the airway showing significant soft tissue swelling and edema to the airway superior to the larynx. The arrows show significant airway narrowing to this soft tissue swelling in the posterior pharyngeal and supraglottic region.

K 50 mg every 8 h. While in the ICU, concern developed for an acute compartment syndrome in his legs because of massive soft tissue hemorrhage and severe coagulopathy. General surgery was consulted, and it was determined that fasciotomy was not necessary. Supportive measures were continued in the ICU with gradual correction of coagulopathy. After an ICU stay of 10 days, his international normalized ratio was still 1.6.

The patient was extubated 4 days before discharge and moved to a general medical floor where he continued to improve. He was given a prescription for 10 oral vitamin K (phytonadione) 5 mg tablets, taken 3 times a day for 7 days, and told to follow up with his primary care physician on an outpatient basis (8). The patient did not return for his outpatient follow-up visit.

DISCUSSION

Patients suffering from BDF poisoning may present with benign bleeding to life-threatening hemorrhage. Unexplained bleeding can be from mild to life-threatening in the form of bruising, nosebleeds, bleeding gums, bleeding disproportionate to injury, hemoptysis, hematuria, vaginal bleeding, gastrointestinal bleeding, intracranial hemorrhage, or hemorrhagic soft tissue swelling (5). An ED work-up will show an elevated international normalized ratio. Further testing may reveal positive blood or urine screen for BDF; however, this test requires advanced testing from a specialized laboratory. These patients typically have no history of coagulopathy and a positive history of synthetic cannabinoid use (5,6). In such cases, vitamin K–dependent coagulopathy should be suspected caused by BDF poisoning and Poison Control Center consultation should be considered (5–10).

There is currently there is no medication for acute reversal of BDF poisoning that has been approved by the U.S. Food and Drug Administration. The mainstay of treatment continues to be oral or intravenous vitamin K. Despite aggressive treatment with vitamin K, the coagulopathy can take days to weeks to resolve (11).

Although most patients with BDF poisoning do not exhibit severe complications, studies have found that when complications do happen they are associated with low serum albumin levels and coingestion of rodenticide and alcohol (12). Though our patient had a history of alcohol use, it is unclear if he coingested alcohol with synthetic cannabinoids.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Emergency physicians should be aware of this outbreak tied to synthetic cannabinoid use and subsequent morbidity and treatment. Other case reports allude to BDF poisoning

that required outpatient management after brief hospital stabilization. However, our case is the first to report severe hemorrhage and the need for prolonged intubation as a result of BDF poisoning. Clinicians should have a high level of suspicion for BDF poisoning when a young patient presents with complaints of bleeding diathesis and any reported history of synthetic cannabinoid use (13).

Acknowledgments—Dr. Ross is an independent contractor for Teleflex and provides clinical education for their products.

REFERENCES

1. European Monitoring Centre for Drugs and Drug Addiction. Understanding the Spice phenomenon. Available at: http://www.emcdda.europa.eu/attachements.cfm/att_80086_EN_Spice%20Thematic%20paper%20—%20final%20version.pdf
2. Nelson ME, Bryant SM, Aks SE. Emerging drugs of abuse. Emerg Med Clin North Am 2014;32:1–28.
3. Kelkar AH, Smith NA, Martial A, Moole H, Tarantino MD, Roberts JC. An outbreak of synthetic cannabinoid-associated coagulopathy in Illinois. N Engl J Med 2018;379:1216–23.
4. Moritz E, Austin C, Wahl M, DesLauriers C, Navon L, Walblay K, et al. Notes from the field: outbreak of severe illness linked to the vitamin K antagonist brodifacoum and use of synthetic cannabinoids – Illinois. March-April 2018. MMWR Morb Mortal Wkly Rep 2018;67:607–8.
5. Hussain N, Hussain F, Haque D, Saeed S, Jesudas R. An outbreak of brodifacoum coagulopathy due to synthetic cannabinoid in central Illinois. Mayo Clin Proc 2018;93:957–8.
6. Powell D. The spice of death: the science behind tainted "synthetic marijuana. Available at: https://www.scientificamerican.com/article/the-spice-of-death-the-science-behind-tainted-synthetic-marijuana/. Accessed January 24, 2019.
7. King N, Tran MH. Long-acting anticoagulant rodenticide (superwarfarin) poisoning: a review of its historical development, epidemiology, and clinical management. Transfus Med Rev 2015;29:250–8.
8. Kruse JA, Carlson RW. Fetal rodenticide poisoning with brodifacoum. Ann Emerg Med 1992;21:331–6.
9. Panigrahi B, Jones BC, Rowe SP. Brodifacoum-contaminated synthetic cannabinoid: clinical and radiologic manifestations of a public health outbreak causing life-threatening coagulopathy. Emerg Radiol 2018;25:715–8.
10. Update—outbreak of life-threatening coagulopathy associated with synthetic cannabinoids use. Available at: https://emergency.cdc.gov/han/han00416.asp. Accessed January 24, 2019.
11. Outbreak alert: potential life-threatening vitamin K-dependent antagonist coagulopathy associated with synthetic cannabinoids use. Centers for Disease Control and Prevention. 2018. Available at: https://content.govdelivery.com/accounts/USCDC/bulletins/1e6dac3. Accessed January 24, 2019.
12. Lee HJ, You MR, Moon WR, Sul H, Chung CH, Park CY, et al. Evaluation of risk factors in patients with vitamin K–dependent coagulopathy presumed to be caused by exposure to brodifacoum. Korean J Intern Med 2014;29:498–508.
13. Outbreak alert update: potential life-threatening vitamin K–dependent antagonist coagulopathy associated with synthetic cannabinoids use. Available at: https://content.govdelivery.com/accounts/USCDC/bulletins/21e1a0f. Accessed January 24, 2019.