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CRITICAL CARE

Adherence to Long-Term Follow-Up of Patients with Life-Threatening, Inhaled Synthetic Cannabinoids-Associated Coagulopathy in Chicago

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Abstract

A large-scale outbreak of life-threatening, inhaled synthetic cannabinoids (Spice/K2)-associated coagulopathy with bleeding complications was recently reported in Illinois. The causative agents were brodifacoum, difenacoum, and bromadiolone, potent, long-acting, 4-hydroxycoumarin anticoagulant rodenticides (LAAR) that were mixed with Spice/K2 products procured and then inhaled by the victims. We report on 3 poisoned patients who reside in underserved, socioeconomically disadvantaged neighborhoods of Chicago that were admitted and treated successfully at two inner-city, tertiary care hospitals in Chicago. The patients were discharged from the hospitals on daily long-term high-dose oral vitamin K_1 (VK_1), provided free of charge. However, 2 patients were lost to follow-up prior to safe discontinuation of oral VK_1 therapy. The third patient was treated and followed successfully for 7 months when VK_1 was discontinued. We conclude that prolonged oral VK_1 therapy and follow-up of acute, life-threatening LAAR poisoning are variable and present challenges to healthcare providers. Appropriate practice guidelines to improve patient access and adherence to daily high-dose oral VK_1 therapy and follow-up should be developed and implemented.

Keywords Rodenticide · Superwarfarins · Brodifacoum · Difenacoum · Bromadiolone · Vitamin K

Introduction

A large-scale epidemic of life-threatening, inhaled synthetic cannabinoids (Spice/K2)-associated coagulopathy with bleeding complications was reported in Illinois, including Chicago, in March 2018. It resulted in 164 poisoned patients and 4 fatalities [1, 2]. Laboratory tests of Spice/K2 specimens confiscated from the victims revealed several synthetic cannabinoids, predominantly AMB-FUBINACA and FUB-APINACA, and three potent, long-acting, second-generation, lipophilic 4-hydroxycoumarin anticoagulant rodenticides (LAAR), brodifacoum, difenacoum, and bromadiolone [2, 3]. Apparently, these toxicants were mixed with various synthetic cannabinoids products procured and then inhaled by the victims [1, 2]. The reason(s) underlying this practice has not yet been divulged by law enforcement agencies investigating this epidemic.

Like warfarin, LAAR inhibit vitamin K epoxide reductase (VKOR) in hepatocytes leading to uncarboxylated (inactive) vitamin K-dependent coagulation factors and bleeding complications [3, 4]. In contrast to warfarin, however, potency of brodifacoum, the most common LAAR isolated in this outbreak, is 100-fold higher and its elimination half-life is much longer (weeks to months) than those of warfarin [3–5].

The predominantly presenting bleeding manifestations in poisoned patients were gross hematuria, gastrointestinal bleeding, and epistaxis [1, 2, 6, 7]. Treatment in emergency departments and medical intensive care units consisted of various blood products, factor replacement, and high-dose intravenous and/or oral vitamin K_1 to stabilize the victims and to control prothrombin time (PT) and International Normalized Ratio (INR) [1, 2, 4, 6, 7]. Once discharged from the hospital, the patients were prescribed high-dose oral vitamin

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K_1 (VK_1, ~ 100 mg daily) for several months along with weekly INR determinations and close follow-up [1, 2, 5–8].

Unfortunately, prolonged oral VK_1 therapy during the post-exposure maintenance phase is very expensive with an estimated retail price of ~ $30,000 per month for cash-paying patients in the USA raising concern for non-adherence of poisoned patients with no or inadequate health insurance [6]. To address this issue, Illinois Department of Public Health secured a large donation of US FDA-approved VK_1 tablets (each, 5 mg) that was made available free of charge to poisoned patients in Illinois throughout the duration of their post-exposure treatment [9]. The long-term outcomes of patients with life-threatening, inhaled synthetic cannabinoids-associated coagulopathy with bleeding complications, who reside in underserved, socioeconomically disadvantaged neighborhoods of Chicago, Illinois have not been reported so far. The purpose of this study is to describe our experience with long-term follow-up of 3 such patients.

Methods

Medical records of 3 patients hospitalized in March 2018 for life-threatening, inhaled synthetic cannabinoids-associated coagulopathy with bleeding complications at the University of Illinois Hospital ($n = 2$) and Jesse Brown VA Medical Center (JBVAMC; $n = 1$) in Chicago, Illinois were reviewed. Pertinent data of hospital course and post-discharge treatment with oral VK_1 along with follow-up were abstracted. A report on treatment of a poisoned male patient in the Emergency Department of JBVAMC has recently been published [7].

Results

All 3 poisoned patients presented with bleeding manifestations in the latter part of March 2018. Circulating brodifacoum and difenacoum were detected in all 3 cases by qualitative high-performance liquid chromatography/tandem mass spectrometry assay (NMS Labs, Willow Grove, PA; limit of detection, 10 ng/ml).

A 26-year-old female reported menorrhagia, expanding thigh bruise, and oral mucosa bleeding. A 32-year-old male complained of hematuria, rectal bleeding, melanotic stools, and epistaxis, and a 63-year-old male reported hematuria, hematochezia, and hemoptysis. INR was unmeasurable in all 3 patients. Initially, they were treated with blood products and intravenous VK_1 and high-dose oral VK_1 (150 mg daily). Bleeding manifestations improved and INR returned to baseline values within 24 h. They were closely monitored and discharged from the hospital 7–8 days after admission. The female patient was discharged on oral VK_1 50 mg daily, provided to her free of charge. In addition, medroxyprogesterone acetate was administered intramuscularly as an effective contraceptive method. She was followed for 83 days without experiencing bleeding manifestations. Given normal INR values on repeated determinations, oral VK_1 was tapered to 15 mg daily. However, she subsequently was lost to follow-up prior to discontinuation of VK_1 and repeated INR determinations. The 32-year-old male was discharged on oral VK_1 50 mg daily, also provided free of charge. However, he was lost to follow-up within 23 days after discharge from the hospital without further INR determinations. The 63-year-old male was discharged on oral VK_1 120 mg daily that was provided free of charge. The patient was closely followed by his primary care physician and reported no bleeding manifestations over the ensuing 6 months. INR was monitored periodically by the anticoagulation clinic. However, taper of VK_1 dose was prolonged because the patient missed several outpatient clinic appointments. Oral VK_1 (100 mg daily) was discontinued 4 weeks later when he reported no bleeding manifestations when seen in clinic. INR was within normal limits (0.93).

Discussion

The major conclusion of this study is that prolonged oral VK_1 therapy and follow-up of acute, life-threatening LAAR poisoning are variable and present challenges to healthcare providers even when VK_1 tablets are provided to patients free of charge.

Although the reasons underlying these outcomes are uncertain, they may be related, in part, to homelessness, irregular access to healthcare services, substance use disorder, and low socioeconomic status of poisoned patients. For instance, lack of health insurance and prohibitive cost of VK_1 tablets delayed hospital discharge of a young woman with life-threatening, inhaled synthetic cannabinoids-associated coagulopathy with bleeding complications [6].

Additional concerns that emerged from our encounters are noteworthy. First, current standard of care emphasizes monitoring INR as biomarker of adequate response to and discontinuation of high-dose oral VK_1 therapy during the maintenance phase [1, 2, 4, 8]. However, INR is not a sensitive index of the salutary effects of VK_1 in extrahepatic organs where 4-hydroxycoumarin anticoagulants also accumulate, particularly when serum/plasma concentrations of brodifacoum and other superwarfarins are undetectable (< 10 ng/ml) [2, 8, 10]. To this end, Wang et al. [11] reported recently on a patient with non-hemorrhagic bromadiolone poisoning (INR, 8.62) who presented with dizziness, unsteady gait, and abnormal behavior. MRI imaging revealed diffuse protein-containing lesions without hemorrhage. The patient was treated with long-term oral VK_1. In

addition, Kalinin et al. [12] showed that brodifacoum accumulates in the rat brain and elicits distinct chronic neuroinflammation and neuropathology.

Although no extrahepatic organ damage was reported in our patients, specific circulating biomarkers of VK metabolism, such as ratio of circulating vitamin 2–3 epoxide to VK and uncarboxylated osteocalcin, may be considered when tapering and discontinuing oral VK_1 therapy during follow-up of poisoned patients.

Second, the long half-life of superwarfarins in the human body, brodifacoum in particular, could have deleterious effects on pregnancy outcomes in poisoned women in childbearing age [13–15]. It is well-established that 4-hydroxycoumarins cross the placenta readily and inhibit synthesis of vitamin K-dependent proteins in the liver and extrahepatic tissues of the fetus [16]. This, in turn, could lead to spontaneous abortion and embryopathy during the first trimester and CNS abnormalities, fatal hemorrhage, and stillbirth at any stage during pregnancy [13–16]. In addition, safety of prolonged, off-label administration of daily pharmacologic doses (~ 100 mg) of oral VK_1 in pregnant women and their fetuses has not been established [17–19]. For instance, fetal health may be susceptible to redox-modulating effects of menadione, an endogenous metabolite of oral VK_1, that elaborates tissue-damaging reactive oxygen species [20, 21]. In addition, safety of prolonged, daily high-dose oral VK_1 in children and adolescents with life-threatening, inhaled synthetic cannabinoids-associated coagulopathy with bleeding complications has not been investigated [19]. As such, appropriate precautions were taken in our female patient.

Last, daily ingestion of 20–30 VK_1 tablets (100–150 mg) for several months may predispose poisoned patients to nonadherence with treatment. Conceivably, safe and efficacious FDA-approved drugs co-administered with oral VK_1 during follow-up that accelerate elimination of superwarfarins from the human body over a relatively short period of time could be beneficial in improving patient adherence by reducing the duration of oral VK_1 therapy. For instance, Cohn et al. [22] showed that treatment with oral cholestyramine, an FDA-approved, safe and efficacious, gut-restricted, anion-exchange resin indicated for the treatment of hypercholesterolemia, significantly reduced the half-life of chlordecone, a lipophilic organochlorine pesticide, in blood and fat of industrial workers that were exposed to substantial amounts of this toxin for several months. To this end, oral cholestyramine has been recently shown to reduce mortality of rabbits with acute brodifacoum poisoning [23].

In summary, prolonged oral VK_1 therapy and follow-up of acute, life-threatening LAAR poisoning are variable and present challenges to healthcare providers. Appropriate practice guidelines to improve patient access and adherence to daily high-dose oral VK_1 therapy and follow-up should be developed and implemented.

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Compliance with Ethical Standards

Conflict of interest Drs. Rubinstein and Feinstein are co-founders of EnSol Therapeutics, LLC.

Research Involving Human Rights This article does not contain any studies with human participants performed by any of the authors.

References

1. Moritz E, Austin C, Wahl M et al (2018) Notes from the field: outbreak of severe illness linked to the vitamin K antagonist brodifacoum and use of synthetic cannabinoids—Illinois. MMWR Morb Mortal Wkly Rep 67:607–608
2. Devguna J, Rasina A, Kima T et al (2018) Outbreak of coagulopathy associated with synthetic cannabinoid use (abstract). Clin Toxicol (Phila) 56:923–924
3. Feinstein DL, Akpa BS, Ayee MA et al (2016) The emerging threat of superwarfarins: history, detection, mechanisms, and countermeasures. Ann N Y Acad Sci 1374:111–1122
4. Caravati EM, Erdman AR, Scharman EJ et al (2007) Long-acting anticoagulant rodenticide poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 45:1–22
5. Lipton RA, Klass EM (1984) Human ingestion of a 'superwarfarin' rodenticide resulting in a prolonged anticoagulant effect. JAMA 252:3004–3005
6. Micula-Gondek W, Ruales V, Zorn C, Angelino A (2019) Synthetic cannabinoid-associated coagulopathy: case report. Psychosomatics 60:211–215. https://doi.org/10.1016/j.psym.2018.05.010
7. Doyle RJ, Elfessi Z, Kolman K (2018) Fixed dose 4-factor prothrombin complex concentrate for bleeding caused by long acting anticoagulant rodenticides. Am J Emerg Med 36:1922.e3–1922.e4
8. Rubinstein I, Weinberg W, van Breemen R et al (2018) Treatment for long acting anticoagulant rodenticide poisoning—beyond INR monitoring? Toxicol Commun 2:59–61
9. http://www.dph.illinois.gov/topics-services/prevention-wellness/medical-cannabis/synthetic-cannabinoids. Accessed 15 Dec 2018
10. Wen L, Chen J, Duan L et al (2018) Vitamin K-dependent proteins involved in bone and cardiovascular health (Review). Mol Med Rep 18:3–15
11. Wang M, Yang Y, Hou Y et al (2017) Effects of bromadiolone poisoning on the central nervous system. Neuropsychiatr Dis Treat 13:2297–2300
12. Kalinin S, Marangoni N, Kowal K et al (2017) The long-lasting rodenticide brodifacoum induces neuropathology in adult male rats. Toxicol Sci 159:224–237
13. Zurawski JM, Kelly EA (1997) Pregnancy outcome after maternal poisoning with brodifacoum, a long-acting warfarin-like rodenticide. Obstet Gynecol 90(Pt 2):672–674
14. Ma M, Zhang M, Tang X et al (2017) Massive neonatal intracranial hemorrhage caused by bromadiolone. A case report. Medicine 96(45):e8506

15. Yan J, Shi Y, Sun C et al (2013) Vitamin K treatment of brodifacoum poisoning in a pregnant woman. Int J Gynaecol Obstet 122:162–163
16. Mehndiratta S, Suneja A, Gupta B et al (2010) Fetotoxicity of warfarin anticoagulation. Arch Gynecol Obstet 282:335–337
17. Kazzi NJ, Ilagan NB, Liang K-C et al (1990) Placental transfer of vitamin K1 in preterm pregnancy. Obstet Gynecol 1990(75):334–337
18. Shahrook S, Erika Ota E, Hanada N et al (2018) Vitamin K supplementation during pregnancy for improving outcomes: a systematic review and meta-analysis. Sci Rep 8:11459
19. https://www.bauschhealth.com/Portals/25/Pdf/PI/Mephyton-PI.pdf. Accessed 10 Dec 2018
20. Thijssen HHW, Vervoort LMT, Schurgers LJ et al (2006) Menadione is a metabolite of oral vitamin K. Br J Nutr 95:260–266
21. Loor G, Kondapalli J, Schriewer JM et al (2010) Menadione triggers cell death through ROS-dependent mechanisms involving PARP activation without requiring apoptosis. Free Radic Biol Med 49:1925–1936
22. Cohn WJ, Boylan JJ, Blanker RV et al (1978) Treatment of chlordecone (Kepone) toxicity with cholestyramine. Results of a controlled clinical trial. N Engl J Med 298:243–248
23. Lindeblad M, Lyubimov A, van Breemen R et al (2019) The bile sequestrant cholestyramine increases survival in a rabbit model of brodifacoum poisoning. Toxicol Sci 165:389–395