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Synthetic cannabinoid-associated coagulopathy secondary to long-acting anticoagulant rodenticides

Observational case series and management recommendations

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Abstract

Synthetic cannabinoids have become increasingly popular drugs of abuse due to low cost and inability to detect these substances on routine drug screenings. In the United States, incidence of synthetic cannabinoid contamination with long-acting anticoagulant rodenticides (LAARs) resulting in coagulopathy and bleeding complications has been described.

We sought to describe the natural history, management approach, and outcomes of bleeding secondary to synthetic cannabinoid-associated LAAR toxicity in an observational case series of patients evaluated at an urban academic medical system.

We conducted an observational study of patients with suspected exposure to LAAR-contaminated synthetic cannabinoids and associated bleeding treated within the Johns Hopkins Health System.

In this 16 subject cohort, hematuria was the most common bleeding symptom at presentation. The majority of the cohort (75%) had international normalized ratio (INR) > 9.6 at presentation. Of the 13 patients with brodifacoum testing, 12/13 (92%) were positive. Twelve patients (75%) had at least 1 INR value below 2 within 24 hours of the first INR measurement. Of this cohort, 1/16 (6%) died in hospital. The median length of hospital stay was 4 days, (interquartile range = 3–6). The average cost of pharmacological treatment for coagulopathy during inpatient hospitalization was $5300 (range, $2241–$8086).

In patients presenting with unexplained coagulopathy it is important for emergency department providers to consider LAAR intoxication and consider formal testing for brodifacoum to assist with treatment planning. Use of a standardized management algorithm including intravenous/oral vitamin K, judicious use of blood products and close laboratory monitoring is essential to optimizing outcomes.

Abbreviations: aPTT = activated partial thromboplastin time, AWP = average wholesale price, CT = computed tomography, FDA = Food and Drug Administration, FFP = fresh frozen plasma, GGC = γ-glutamyl carboxylase, ICH = intracerebral hemorrhage, INR = international normalized ratio, ISTH = International Society on Thrombosis and Haemostasis, LAAR = long-acting anticoagulant rodenticide, PCCs = prothrombin complex concentrates, PT = prothrombin time, VKOR = vitamin K epoxide reductase.

Keywords: brodifacoum, coagulopathy, K2, long-acting anticoagulant rodenticides, synthetic cannabinoids, treatment algorithm, vitamin K

1. Introduction

Synthetic cannabinoids commonly called "K2" or "Spice," are psychoactive compounds marketed as marijuana alternatives, and are listed as Schedule I substances under the Controlled Substances Act.[1,2] These products are considered attractive alternatives to marijuana for users because they are relatively inexpensive and not detected in routine drug testing. The supply chain of this recreational substance is unregulated, resulting in variable product composition and widespread availability.[1] There is limited information in the currently published literature describing the direct effects of synthetic cannabinoids on the body, however these substances appear to have more dangerous and severe health effects than associated with marijuana.[3] The case in Box 1 (see Box 1, http://links.lww.com/MD/D211, Supplemental Content, which illustrates the case report of patient 13 including two images of her head computed tomography [CT] scan) highlights one such patient experience and in July 2018 the Food and Drug Administration (FDA) published press release stating that hundreds of patients were hospitalized after consumption of synthetic cannabinoids identified to be contaminated with

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brodifacoum and other long-acting anticoagulant rodenticides (LAARs).[4] On this press release it is suggested that LAAR contamination (primarily brodifacoum) of synthetic cannabinoids is done intentionally by producers under the assumption that it increases the potential of the psychoactive effects of these drugs.[4] In the United States, several geographic regions have been affected by an epidemic of LAAR toxicity due to use of contaminated synthetic cannabinoids.[5]

Long acting anticoagulant rodenticides directly bind to and inhibit vitamin K epoxide reductase (VKOR). This leads to the depletion of vitamin K1 stores and its reduced form, vitamin K hydroquinone. In the absence of vitamin K hydroquinone, the enzyme γ-glutamyl carboxylase (GGC) cannot carboxylate and activate the vitamin K-dependent coagulation factors II, VII, IX, and X, and the regulatory proteins C, S, and Z.[6,7] Factors II and X are part of the common pathway of the coagulation pathway, thus the depletion of these factors results in prolongation of the activated partial thromboplastin time (aPTT) and prothrombin time (PT).[8] Exogenous administration of vitamin K can restore GGC activity, effectively treating the coagulopathy.

The optimal management of LAAR toxicity is not well defined, and treatment is complicated by the long half-life and potency (up to 100 times more than warfarin) of these substances.[7] These characteristics make clinical management of suspected LAAR toxicity challenging. Treatment is similar to managing warfarin over-exposure, and includes administration of prothrombin complex concentrates (PCCs) or fresh frozen plasma (FFP) with vitamin K.[9] The most appropriate dose and treatment duration of vitamin K for the management of brodifacoum or other LAAR toxicity remains unclear.

In response to this uncertainty and a series of early cases presenting to our institution, a multidisciplinary team of pharmacists and hematologists developed the Johns Hopkins protocol for the management of suspected LAAR exposure. We summarize outcomes from a series of patients with suspected or confirmed LAAR toxicity, and experience with the application of our health system's treatment algorithm for the management of this condition.

2. Materials and methods

This is observational study is a retrospective review of consecutive patients presenting to The Johns Hopkins Health System with suspected LAAR exposure between April and September 2018. Subjects were included in this analysis if they had bleeding and clinically suspected toxicity from use of LAAR-contaminated synthetic marijuana. Subjects were excluded if they were prescribed warfarin prior to admission. Elevated international normalized ratio (INR) at the time of presentation without other obvious provoking factors was the primary criterion for consideration of LAAR toxicity. Confirmatory testing for brodifacoum exposure was ordered at the discretion of the primary provider at the time of hospitalization and sent to NMS Laboratory (Willow Grove, PA) for processing. The upper limit of quantification for the INR varied among individual institutions within our health system. The lowest upper limit of detection was 9.6; thus, all INR results above this value were reported as >9.6.

An institutional treatment protocol (Fig. 1) was developed to aid in the management of patients with suspected LAAR toxicity, but protocol adherence was not mandatory. Because this protocol was developed at a hospital with an INR upper limit of quantification of 12, an INR value of >10 was utilized to identify patients at risk for spontaneous bleeding and in need of rapid INR correction with intravenous vitamin K. For both inpatient and outpatient management, the primary goals of treatment were to achieve hemostasis and to maintain an INR below 2. Maryland Poison Control was involved in determining the initial doses of vitamin K at presentation and followed the patients' outcomes throughout the hospital stay and into the

Presentation	Initial Treatment	Maintenance Treatment	Laboratory Monitoring	Recommended Long-Term Follow-up
• No active bleeding • INR ≥ 1.4-9.9	• Vitamin K 50 mg PO once†	• Vitamin K 50 mg PO q8h† • Titrate dose according to serial INRs and achievement of hemostasis	• **Initially**: every 6 hour INR, aPTT, CBC • Space labs to every 12 to 24 hours as vitamin K is tapered	• Obtain brodifacoum level at time of presentation • Consider scheduling follow-up with The Johns Hopkins Hematology Anticoagulation Clinic
• No active bleeding • INR ≥ 10	• Vitamin K 20 mg IV **ONCE** with vitamin K 50 mg PO	• Vitamin K 50 mg PO q8h† • Titrate dose according to serial INRs and achievement of hemostasis		
• Mild bleeding (e.g. epistaxis, oral mucosal bleeding, mild hematuria, etc.) **AND** • INR ≥1.4	• Vitamin K 20 mg IV **ONCE** with vitamin K 50 mg PO	• Vitamin K 50 mg PO q6h† • Titrate dose according to serial INRs and achievement of hemostasis		
• Moderate bleeding (bleeding not meeting the criteria for mild or severe) **AND** • INR ≥ 1.4	• Vitamin K 20 mg IV **ONCE** with vitamin K 50 mg PO • Administer 10-15 mL/kg FFP	• Vitamin K 50 mg PO q6h† • Titrate dose according to serial INRs and achievement of hemostasis		
• Life threatening bleeding (intracranial hemorrhage, cardiac tamponade, bleeding requiring initiation of massive transfusion protocol, pulmonary hemorrhage, or other critical bleeding) **AND** • INR ≥ 1.4	• Administer prothrombin complex concentrate, dosed according to patient's weight and INR at presentation* • Administer vitamin K 20 mg IV **ONCE** with vitamin K 50 mg PO	• Vitamin K 50 mg PO q6h† • Titrate dose according to serial INRs and achievement of hemostasis		

*Dosing recommendations can be found in Epic order

† IV vitamin K can be used instead of PO vitamin K for patients without enteral access or who are NPO

Pharmacy Instructions:

- Oral vitamin K doses > 10 mg should be prepared and dispensed using vitamin K IV solution in an oral syringe. For patients unable to tolerate the taste of the IV vitamin K formulation administered enterally, the solution can be diluted by nursing in 20-30 mL of orange juice immediately prior to administration.
- IV vitamin K doses > 25 mg should be prepared in 50 mL and administered over 60 minutes to reduce the risk of hypersensitivity reactions

Figure 1. Suspected long-acting anticoagulant rodenticides (LAAR) toxicity treatment protocol. aPTT = activated partial thromboplastin time, FFP = fresh frozen plasma (FFP), INR = international normalized ratio, IV = intravenous administration, NPO = nothing by mouth, PCC = prothrombin complex concentrate, PO = Oral administration.

outpatient phase of care until the patient completed visits or were lost to follow-up. Bleeding severity was scored using the International Society on Thrombosis and Haemostasis (ISTH) criteria.[10,11] The cost per dose of each hemostatic medication administered was calculated based on the average wholesale price (AWP) as follows: $2.77 USD per unit for Kcentra, $1.57 USD for Profilnine, $70.51 USD per 5 mg vitamin K tablet, and $60.30 per 10 mg of vitamin K solution for intravenous administration. The price per unit of FFP was estimated to be $127 USD based on internal communication with our transfusion medicine department. Descriptive statistics were planned for this cohort and data analysis was conducted utilizing SPSS 18 (IBM, Armonk, New York) and Stata 13 (Statacorp, College Station, Texas). The study was approved by the Johns Hopkins Institutional Review Board.

3. Results

In this series, 16 patients with suspected LAAR toxicity were identified over the 6-month period, with a peak number of patients (n = 6) in April. The mean age at presentation was 36 years (standard deviation [SD] = 8) and 6 (38%) were women. The most common bleeding symptoms at the time of presentation were hematuria (n = 13), hematemesis (n = 6), epistaxis (n = 5), and oropharyngeal bleeding (n = 5), while the most severe bleeding presentation was intracranial hemorrhage (n = 1). The first INR obtained after presentation was >9.6 in 12 patients (75%). Fourteen patients (88%) were admitted to the hospital. The 2 subjects not admitted were referred to the emergency department due to hospitalization of a family member for coagulopathy after similar use of synthetic cannabinoids. Table 1 summarizes patient characteristics.

Table 1

Patient characteristics.

Characteristic	Patients
Age, y [mean ± SD]	36 ± 8
Gender (n [%])	
Female	6 (37.5%)
Male	10 (62.5%)
Race (n [%])	
Black	6 (37.5%)
White	8 (50.0%)
Other	2 (12.5%)
Weight, kg (n [%])	
40–60	6 (37.5%)
60–80	5 (31.3%)
80–100	3 (18.8%)
100–120	1 (6.3%)
Unknown	1 (6.3%)
BMI, kg/m^2 (n [%])	
<18.5	3 (18.8%)
18.5–24.9	8 (50.0%)
25.0–29.9	3 (18.8%)
30.0–34.9	0
35.0–39.9	1 (6.3%)
Unknown	1 (6.3%)
Length of stay, d (n [%])	
0–2	4 (25.0%)
3–5	7 (43.8%)
6–8	3 (18.8%)
9–11	1 (6.3%)
12–14	1 (6.3%)
Insured at admission (n [%])	14 (87.5%)

The mean hemoglobin at presentation was 13.4 g/dL (SD = 2.2). Among the subjects treated with vitamin K, the median total inpatient dose of intravenous and oral vitamin K was 20 mg (interquartile range [IQR] = 15–32.5) and 327.5 mg (SD = 150–497.5), respectively. Nine patients with bleeding on presentation received a median dose of 1 unit of FFP (IQR = 1–2), and 3 were treated with PCC. Table 2 summarizes patient clinical presentation and hospital course. Initial and ongoing management varied by the severity of bleeding at presentation and degree of INR elevation as outlined in the treatment

Table 2

Presentation and hospital course.

Characteristic	Patients
Brodifacoum level obtained (n [%])	13 (81.3%)
Brodifacoum level detectable (n [%])	12 (92.3%)
Bleeding presentation (n %)	14 (87.5%)
Epistaxis	5 (35.7%)
Muscle hematoma	3 (21.4%)
Bruising	4 (28.6%)
Hematemesis	6 (42.9%)
Hematochezia	2 (14.3%)
Hematuria	13 (92.2%)
Hemoptysis	4 (28.6%)
Intracranial hemorrhage	1 (7.1%)
Heavy menorrhagia	1 (7.1%)
Oropharyngeal	5 (35.7%)
Bleeding severity	
ISTH major bleeding (n [%])	5 (35.7%)
Score 1	1 (20.0%)
Score 2	3 (60.0%)
Score 3	1 (20.0%)
ISTH CRNM bleeding (n [%])	9 (64.3%)
Coagulation parameters at presentation	
INR (n [%])	
<1.5	0
1.5–3.0	0
3.1–5.5	2 (12.5%)
5.6–9.5	2 (12.5%)
≥9.6	12 (75.0%)
aPTT (s) (n [%])	
22.9–30.6	1 (6.3%)
30.7–60	2 (12.5%)
61–90	3 (18.8%)
91–120	4 (25.0%)
121–150	1 (6.3%)
151–180	0
181–200	2 (12.5%)
>200	2 (12.5%)
Unknown	1 (6.3%)
Hemoglobin, g/dL (mean ± SD)	13 ± 2
Hematocrit (%) (median [IQR])	41.3 (37.7–43.1)
Platelet count (K/mm^3) (median [IQR])	234.5 (213.5–247.0)
Aspartate aminotransferase (Units/L) (n = 13) (median [IQR])	25.0 (19.8–37.0)
Alanine aminotransferase (Units/L) (n = 12) (median [IQR])	20.0 (16.0–25.0)
Total patients that were prescribed vitamin K at discharge (n [%])	14 (87.5%)
Total vitamin K regimen prescribed (mg/d) (median [IQR])	50.0 (50.0–100.0)
Coagulation parameters at discharge	
INR (n [%])	
<1.5	13 (81.3%)
1.5–3.0	1 (6.3%)
3.1–5.5	1 (6.3%)
5.6–9.5	1 (6.3%)
≥9.6	0

aPTT = activated partial thromboplastin time, CRNM = clinically relevant non-major, INR = international normalized ratio, IQR = interquartile range, ISTH = International Society on Thrombosis and Haemostasis.

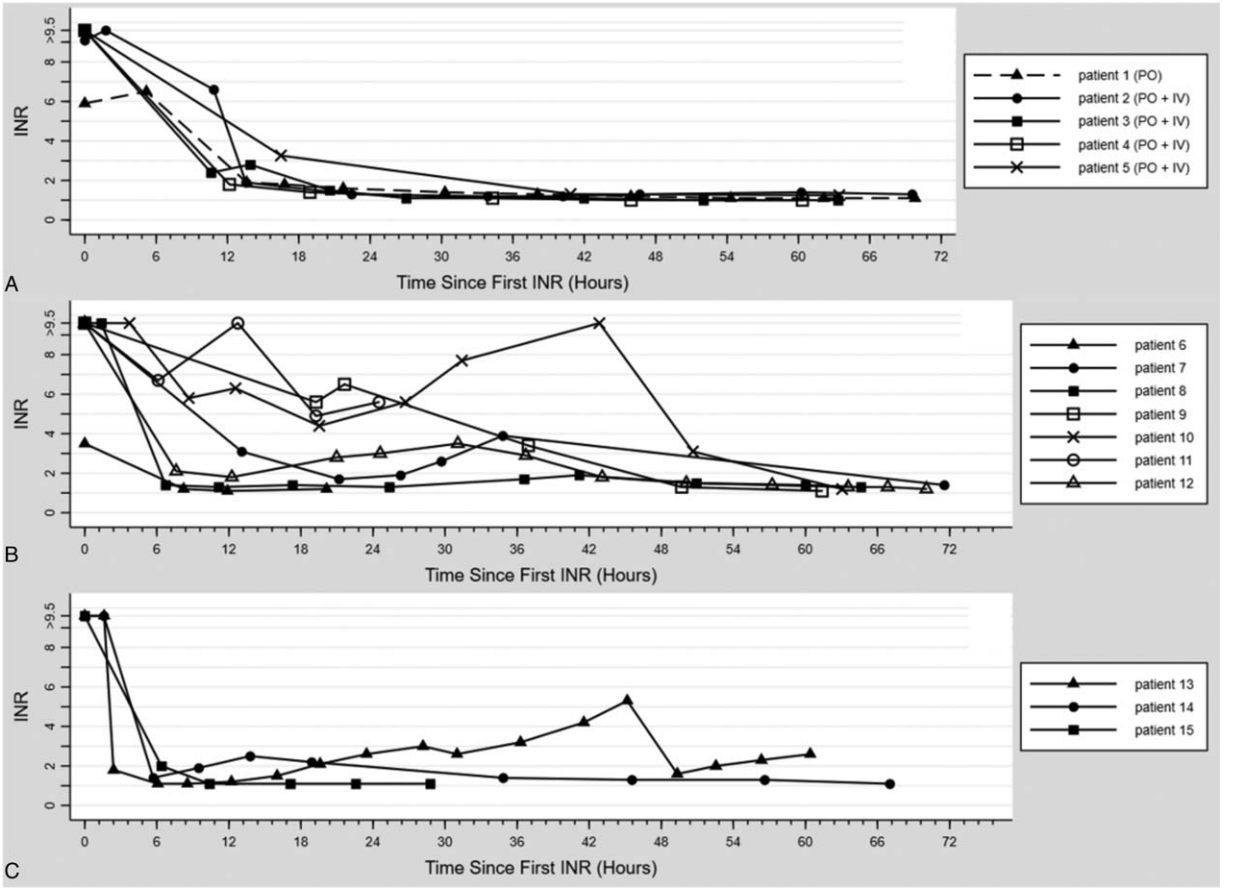

Figure 2. Inpatient international normalized ratio (INR) trends by individual patient. Panel A includes patients who only received vitamin K (intravenous and/or oral); Panel B includes patients who received both vitamin K (intravenous and/or oral) and fresh frozen plasma; and Panel C includes patients who received vitamin K (intravenous and/or oral) with prothrombin complex concentrate. INR = international normalized ratio, IV = intravenous administration, PO = oral administration.

protocol (Fig. 1). INR trends over time according to intervention group are depicted in Fig. 2. INRs were more labile in the group of patients receiving vitamin K (intravenous and/or oral) with FFP than patients receiving vitamin K alone, or vitamin K with PCC.

INR trends and pharmacologic interventions are depicted for 4 select patients in Fig. 3. Patients 4 and 8 received oral and intravenous vitamin K at doses and administration frequencies closely matching the treatment protocol (Fig. 1). Patients 8 and 10 both presented with hematemesis and hematuria after synthetic cannabinoid exposure, and received FFP with oral and intravenous vitamin K administration. However, the graph for patient 10 depicts INR elevation during a period of delayed vitamin K administration. Upon resumption of vitamin K 50 mg administered orally every 8 hours, his INR normalized. The INR trend and interventions for patient 13, the patient described in Box 1 (see Box 1, http://links.lww.com/MD/D211, Supplemental Content, which illustrates the case report of patient 13 including 2 images of her head computed tomography [CT] scan). No patients in this cohort experience adverse effects as a result of high dose vitamin K exposure.

Clinical outcomes included 1 death due to intracerebral hemorrhage (ICH) (patient 13), 3 self-discharges against medical advice, 1 administrative discharge, and 11 discharges in stable clinical condition. The median length of stay was 4 days (IQR = 3–6). The average cost of pharmacologic hospital treatment was $5300 USD (range $2241–$8086 USD).

Of this cohort, synthetic cannabinoid use was confirmed via patient and family interviews in 14 (88%) patients, with 8 patients (57%) reporting the last use within 48 hours prior to hospital admission. Thirteen patients (81%) had confirmatory brodifacoum testing, and brodifacoum levels returned detectable levels in 12 cases (92%). Although the brodifacoum assay returned negative for 1 patient, he was treated for superwarfarin toxicity due to his lack of concomitant comorbidities and presence of coagulopathy on presentation refractory to standard doses of vitamin K.

Fourteen patients (87.5%) were prescribed vitamin K at discharge. Patients without discharge vitamin K prescriptions included the patient with fatal intracranial hemorrhage, and the patient who left against medical advice. Eight patients were scheduled for ongoing INR monitoring with vitamin K adjustment at the outpatient hematology anticoagulation clinic. Of the 8 patients that followed in the hematology anticoagulation clinic, the duration of follow-up was 35 days on average (range, 13–84). Five patients required an increase in their outpatient dose of vitamin K at the first follow-up visit to maintain an INR below 2. All 8 patients were lost to follow-up despite multiple attempts from the anticoagulation clinic team to re-establish care using various forms of communication. Two episodes of re-bleeding occurred after discharge secondary to poor medication adherence in the outpatient setting.

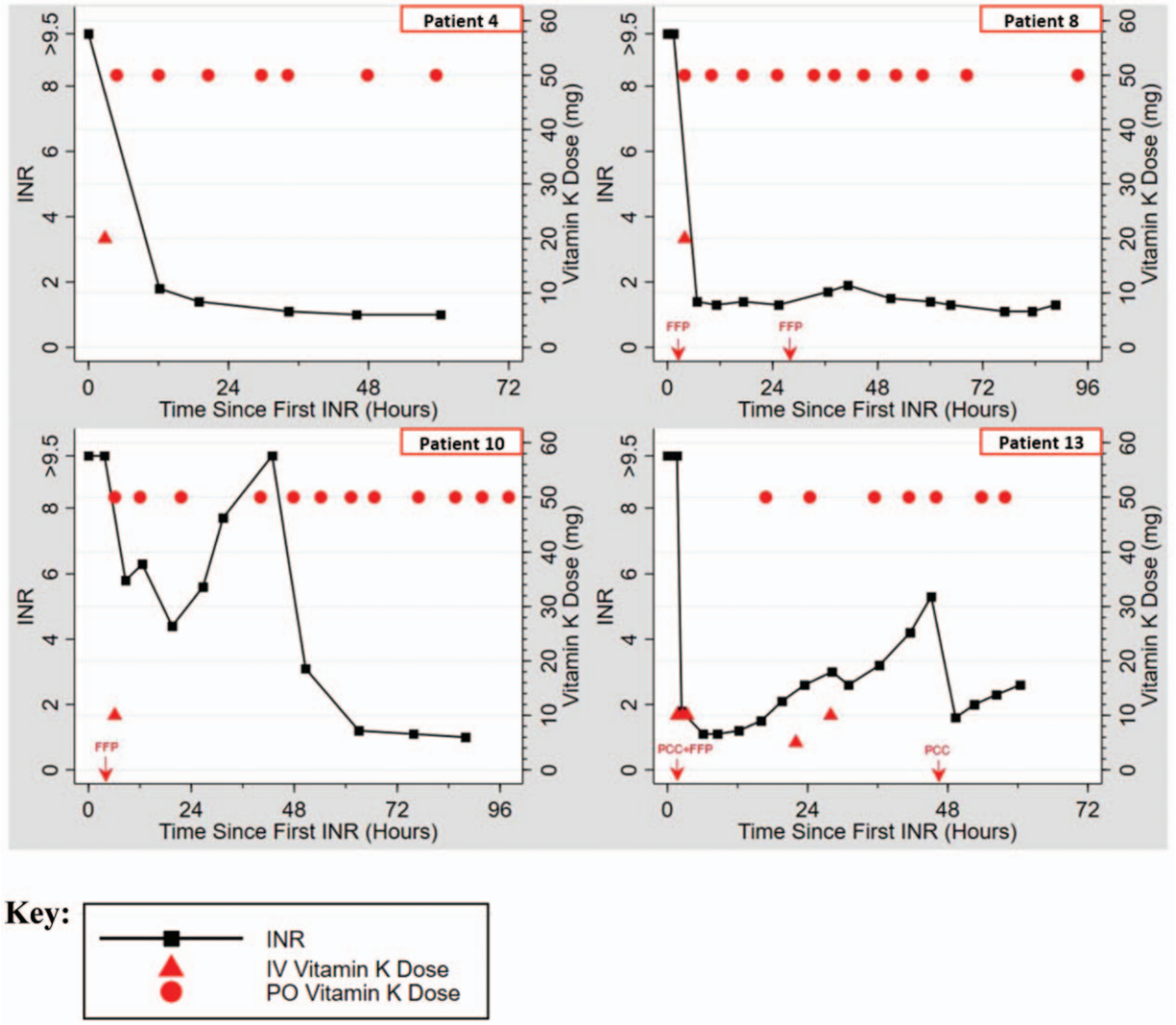

Figure 3. International normalized ratios (INRs) and interventions over time for select inpatients. Patient 4 received vitamin K only (intravenous and oral); patients 7 and 10 received vitamin K (intravenous and oral) and fresh frozen plasma (FFP); patient 13 received vitamin K (intravenous and oral), fresh frozen plasma, and prothrombin complex concentrate (PCC). INR = international normalized ratio, IV = intravenous administration, FFP = fresh frozen plasma, PCC = prothrombin complex concentrate, PO = oral administration.

4. Discussion and conclusions

4.1. Interpretation

In this series we provide clinical outcomes of a cluster of patients presenting with LAAR coagulopathy and expert based approach to treatment of such patients at our academic center. In this cohort, patients most commonly presented with hematuria and/or epistaxis. Twelve patients (75%) achieved at least one INR value below 2 within 24 hours of the first INR measurement. Three of the 4 patients without an INR value below 2 within 24 hours of the first INR measurement underwent a treatment approach inconsistent with recommendations outlined in the treatment protocol. Of note, the 3 patients with protocol non-adherence and inadequately reversed INRs within 24 hours of presentation received insufficient vitamin K doses. The one fatality was in a patient presenting with intracerebral hemorrhage with brain herniation at the time of emergency department presentation. We believe that rapid diagnosis of these coagulopathies, and initiation of a vitamin K based treatment regimen that is continued for a prolonged period is essential to avoidance of severe clinical complications. Therefore, detection of clinical symptoms of LAAR-induced coagulopathy must be recognized in a variety of settings.[1]

Our protocol was developed with a multi-disciplinary team of hematologists and clinical pharmacists after the first LAAR-toxicity case at our health system. Recommendations were compiled based on knowledge of superwarfarin action and after an extensive literature review of existing data describing LAAR-toxicity management.[10–23] This information was then disseminated to clinicians and pharmacists at our institution. A treatment protocol assists with expediting care in across all setting of our health system.

Brodifacoum and other superwarfarins are LAARs that interfere with hepatic synthesis of vitamin K-dependent coagulation factors (II, VII, IX, X).[12] Coagulopathy reversal for LAARs is achieved with similar strategies to warfarin reversal, (PCC or

FFP administered with vitamin K).[13] PCCs reverse warfarin and LAARs by increasing levels of vitamin K-dependent coagulation factors (II, VII, IX, X, protein C and S).[14] Since the vitamin K-dependent coagulation factors in PCC have a limited half-life, it is essential to treat patients with LAAR exposure with concomitant vitamin K and PCC to provide the liver with sufficient vitamin K to resume synthesis of functional vitamin K-dependent coagulation factors. While 10 mg or less of phytonadione is sufficient to reverse warfarin anticoagulation, large daily doses of phytonadione (25–600 mg/d) are required to overcome the effects of brodifacoum due to its greater potency.[1,15–23] Additionally, treatment with high dose vitamin K is required for weeks to months due to the long half-life of LAARs. These factors, combined with available literature, were taken into consideration when developing the LAAR toxicity treatment protocol at our health system.

Vitamin K doses ranging from 25 to 600 mg/d have been required to reverse LAAR-induced coagulopathy in the published literature.[1,15–23] In our treatment protocol, we suggest vitamin K 50 mg every 6 or 8 hours initially depending on whether the patient presented with bleeding symptoms, with further up- or down-titration of the dose based on clinical response. However, we found 50 mg every 8 hour oral dosing to be inadequate in patients 5 and 10, and vitamin K 50 mg orally every 6 hours resulted in inadequate INR lowering in patient 9. This highlights the importance of aggressive vitamin K dosing at the time of presentation and subsequent dose reduction as tolerated. When preparing for discharge, the cost of vitamin K was an additional obstacle. Multiple contacts were made to insurance companies and state agencies in order to be able to obtain sufficient oral vitamin K for each patient to complete their course of treatment.

According to human pharmacokinetic data oral vitamin K administration is associated with a half-life of 6 hours.[24] Additionally, although vitamin K is lipid soluble, there is minimal toxicity associated with administration of high doses. Therefore, we recommend vitamin K 50 mg every 6 hours be initiated on presentation for patients with clinically significant bleeding and initial INRs greater than or equal to 1.4, regardless of the degree of initial INR elevation. The contribution of the frequency and duration of LAAR exposure to the severity and refractoriness of LAAR-induced coagulopathy is unclear. However, because of the lipophilicity and long half-life of LAARs,[1] patients with higher degrees of exposure may require more aggressive initial vitamin K dosing. Although some case reports cite the use of phenobarbital, a potent cytochrome P450 enzyme inducer, to increase LAAR elimination, phenobarbital was not included in our protocol due to the prolonged time to onset of enzyme induction effects, adverse effects, and abuse potential.[1,19]

Further complicating the treatment of LAAR-induced coagulopathy is the lack of readily available laboratory assays to detect and quantify the degree of toxicity. The recent epidemic of LAAR-induced coagulopathy has been primarily due to brodifacoum-tainted synthetic marijuana. Only one reference laboratory in the United States offers a brodifacoum assay (NMS Laboratories; Willow Grove, PA), which is qualitative and takes several days to result. Although a readily available quantitative assay would be helpful for clinical management, an undetectable serum level does not exclude the possibility of brodifacoum toxicity. Due to the lipophilicity and resultant hepatic sequestration of brodifacoum, concentrations in the liver can remain significantly elevated in the setting of undetectable plasma concentrations.[1,20,23] Therefore, we included one patient with a negative serum brodifacoum level, with a clinical presentation and social history consistent with LAAR-induced coagulopathy. We also cannot exclude the possibility that this patient or other patients in our cohort may have been exposed to non-brodifacoum LAARs. In light of these challenges, awareness of the typical demographics and clinical presentations of patients with LAAR-induced coagulopathy is critical to ensure appropriate identification and treatment.

Outpatient management of LAAR-induced coagulopathy is particularly challenging due to the long half-life of these substances and requirement for prolonged treatment. To ensure appropriate transitions of care and longitudinal management of vitamin K dosing, we developed a referral program for LAAR-induced coagulopathy. With this model, patients were scheduled to see a clinical pharmacist in our hematology anticoagulation clinic after discharge. As with other reports,[25] long-term management of this patient population proved challenging even with these arrangements. All patients were lost to follow-up during their outpatient course prior to completing an adequate course of treatment with vitamin K.

There are notable differences between the two published geographic case series of synthetic cannabinoid-induced coagulopathy.[25,26] Kelkar et al[25] described a single tertiary care hospital's experience with managing 34 cases of LAAR-toxicity secondary to synthetic cannabinoid use. Most bleeding events were mild in both series, though the types of bleeding presentations differed slightly; intracerebral hemorrhage, bruising, melena, and menorrhagia were more frequent in the Illinois outbreak. Fewer patients in the Illinois cohort achieved an INR value below 2 within 24 hours of the first INR measurement than with our population, perhaps due to differences in treatment protocols.[25]

Another recent case series published by Armstrong et al[26] discusses the clinical course of 6 patients presenting with multi-organ failure from synthetic cannabinoids exposure. Psychological disturbance, acute kidney injury, severe rhabdomyolysis, compartment syndrome, shock, and liver failure were observed in this cohort, highlighting the wide variability in symptoms and severity after use of synthetic cannabinoids. In this case series, patients were not tested for brodifacoum and interventions to reduce LAAR-coagulopathy and resultant INRs were not described. While these findings were different from ours and the Illinois experience, future studies could consider correlation between LAAR toxicity, symptom type, and symptom severity when reporting outcomes.

Rapid reduction of INR is a clinical priority and therefore we recommend the more aggressive vitamin K dosing strategy utilized in our protocol, with careful de-escalation of dosing according to response. Because the physiology of LAAR-induced coagulopathy is similar to warfarin-induced coagulopathy, we feel it is reasonable to extrapolate from available data demonstrating superiority of PCC administration to FFP for life threatening warfarin-induced hemorrhage to the treatment of LAAR-induced life-threatening bleeding.[27] We did not include recombinant factor VIIa as a treatment option in the Johns Hopkins protocol because of limited available data for this agent for warfarin reversal and high adverse event rates.[27] Additionally, administration of recombinant factor VIIa may lower the INR in patients with LAAR-induced coagulopathy, but due to the short half-life, this effect is likely to be for limited duration, and does not address the underlying deficiency of other vitamin-K dependent clotting factors.

There are several limitations to this paper, the majority of which relate to the small sample size in this cohort. We cannot provide adjustment for comorbidities or analysis within bleeding types due to the small sample size.

Suspected LAAR exposure warrants an expedited approach to clinical assessment and treatment. This case series underscores the need for heightened awareness of this increasingly prevalent etiology for severe bleeding including ICH in emergency departments and system readiness. Targeted and expeditious public health education regarding avoidance of synthetic cannabinoids potentially contaminated with brodifacoum is essential. Health care providers should consider vitamin K-dependent coagulopathy in patients with unexplained bleeding and reported or suspected synthetic cannabinoid use. Geographic areas with increased prevalence of LAAR-induced coagulopathy should consider the development and implementation of a standardized treatment protocol. Although this protocol was developed because of an epidemic of coagulopathy associated with exposure to LAAR-contaminated cannabinoids, it would be appropriate to utilize this protocol for the management of other etiologies of brodifacoum toxicity. Utilization of the Johns Hopkins protocol for LAAR-induced coagulopathy resulted in adequate INR reduction within 24 hours of presentation in 75% of patients and only one fatality.

Author contributions

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