

"MORTAR & PENCIL" CONCORDIA UNIVERSITY WISCONSIN SCHOOL OF PHARMACY WRITING CLUB:

Management of Bleeding Associated with the Use of Brodifacoum Tainted Synthetic Cannabinoids

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Synthetic cannabinoids are chemically synthesized analogs of natural marijuana that contain numerous psychoactive and potentially harmful compounds.¹ Synthetic cannabinoids are recognized under various names such as spice, genie, K2, sence, moon rocks, black mamba, kush, fake marijuana and others.^{2,3} Use of synthetic cannabinoids is appealing for pleasure seekers because it causes a "high" similar to tetrahydrocannabinol (THC), is undetectable in a urine drug screen and is regarded as an alternative to marijuana.⁴ It is readily available in abundant quantities and labeled with subtle names such as "for aromatherapy" or "incense" that can be deceptive to users.^{2,5}

The chemical composition of synthetic cannabinoids is constantly changing and may include other psychoactive ingredients. Mu-opioid agonists and many other miscellaneous chemicals that may have cannabinoid-like, monoamine oxidase inhibitor (MAOI), or hypnotic/anxiolytic activity have been found in these products.⁶ There have been reported cases of myocardial infarction, serious seizures and most recently, unexplained bleeding due to the use of contaminated synthetic cannabinoids.^{2,6,7} Some cases involve accidental ingestion or suicide attempts in patients with mental health disorders.^{8,9}

The Food and Drug Administration (FDA) released a press statement in July 2018 warning about the significant health risk associated with contaminated illegal cannabinoid products.¹⁰ As of May 2018, the Illinois Department of Public Health (IDPH), reported 164 cases in Illinois, including 4 deaths, of severe bleeding among people who have used contaminated

synthetic cannabinoids.¹¹ In Wisconsin, 15 cases have reported to the Wisconsin Department of Health Services (DHS) since March 2018, with 7 confirmed and 8 probable cases.¹² The purpose of this article is to increase pharmacists' awareness of the potential toxicities and harm associated with the use of synthetic cannabinoids and to understand the acute and subacute management of these patients.

Brodifacoum

Synthetic cannabinoids are often contaminated with brodifacoum.³ Brodifacoum is thought to prolong or increase the "high" effect of synthetic cannabinoid.¹³ Brodifacoum falls under the class of long acting anticoagulant rodenticide (LAAR) compounds sometimes called "superwarfarins." These compounds were developed in response to warfarin resistance in the rat population in the 1970s.⁷ LAARs are highly lipophilic, 100-fold more potent than warfarin, undergo enterohepatic circulation and have a more rapid onset of action.⁸ Brodifacoum is the most commonly used rodenticide and has a mechanism of action similar to warfarin. It prevents the carboxylation of the vitamin K – dependent coagulation factors II, VII, IX and X into their active procoagulant form.⁷ The elimination half-life of brodifacoum ranges from 16 to 34 days, compared with 17 to 37 hours for warfarin.⁹ The anticoagulant effects of brodifacoum has been reported to last from 51 days and in some cases up to 9 months after ingestion.^{9,14}

Brodifacoum toxicity is a significant concern because its effect can be present without significant serum concentrations.⁹ In most reported cases, neither patients nor

clinicians were aware of the brodifacoum concentration in the ingested products.⁵ The onset of anticoagulation effects after acute ingestion range from 8 to 48 hours and clinical presentation can be unremarkable during the first twelve hours post-ingestion.^{9,14} Laboratory evidence of coagulopathy occurs within one to two days after ingestion and physical evidence of coagulopathy can be delayed for several days to weeks. If untreated, anticoagulation may continue for months.⁹

Based on published case reports, the clinical presentation of toxicity can range from asymptomatic to active bleeding from any mucosal site or organ, gingival bleeding, epistaxis, ecchymosis, gastrointestinal bleeding, hemoptysis, hematuria, and intracranial bleeding.^{9,13,14} One case of a 46-year-old female presented with gastric hemorrhage and severe coagulopathy, prolonged prothrombin time (PT) and partial thromboplastin time (PTT) both greater than 110 seconds. Her serum level of brodifacoum was markedly elevated at 1302 ng/mL.⁸ Another case of a 36-year-old male presented with low back pain, hematuria, hematemesis, and melena. His initial laboratory test results included an international normalized ratio (INR) > 9, PTT of 102 seconds and prolonged PT greater than 130.⁷ Laboratory results that can indicate brodifacoum toxicity includes the presence of markedly elevated INR, prolonged PT and PTT, presence of brodifacoum in serum using high performance liquid chromatography (HPLC), followed by the demonstration of specific deficiency of vitamin K-dependent blood coagulation proteins.^{8,15,16}



Acute Management of Toxicity

There are no guideline recommendations for the management of bleeding in brodifacoum toxicity. Contact with local Department of Public Health and poison control center is necessary when brodifacoum poisoning is suspected.³ If brodifacoum exposure is suspected or known, the patient should be evaluated for bleeding symptoms and coagulation assay abnormalities.¹³ If no clinical abnormalities are present after 48 hours, patients should be on continued observation without treatment.¹⁴

If clinically major bleeding is present, vitamin K1 10 mg should be administered intravenously in conjunction with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP).⁸ The dose of PCC or FFP administered is not consistent among case reports and often based on presenting symptoms and INR. Initial

doses of FFP administered in case reports ranged from 2 to 6 units.¹³ There is little evidence to support the use of recombinant factor VIIa for this indication.¹⁵ Intravenous vitamin K1 is preferred due to its rapid effect when bleeding is present and urgent intervention is required. Although, there is a risk of anaphylaxis, this has been mitigated in modern preparations, appropriate monitoring for anaphylaxis reactions and diluted administration over 30 minutes.^{14,15}

Once serious bleeding is controlled, intravenous vitamin K1 can be switched to the oral formulation.^{5,8,17} There is the concern of hematoma with intramuscular administration of vitamin K1, therefore, oral is the preferred route.¹³ The dosing of oral vitamin K1 is dependent on the duration of action rather than the half-lives of the clotting factors.⁵ Vitamin K1 has a long duration of action, reported at greater than 168 hours in warfarin-treated patients,

but very little is known about the kinetics of vitamin K1 in brodifacoum toxicity.⁵ The initial dose of vitamin K1 in reported cases of brodifacoum toxicity varies with doses ranging from 10 mg to 420 mg per day.^{5,8,13} Patients may require multiple dose adjustment of vitamin K1 before achievement of a therapeutic dose.¹³

Due to the enterohepatic recycling and long half-life of brodifacoum, there may be rebound bleeding issues in patients with brodifacoum toxicity.⁸ Maintenance therapy with vitamin K1 is continued for extended durations after an injection.¹³ Maintenance dosing from case reports ranges from 15 to 600 mg daily with 100 mg daily being the most common dosage.¹³ Long term use of oral vitamin K1 is often tapered over weeks or months based on coagulation parameters like INR and PT.⁷ If available, serial measurement of brodifacoum levels may be useful in projecting duration of oral vitamin

K1 therapy.¹⁷ Of note, brodifacoum assumes a zero-order kinetics at higher concentrations and then switches to first-order kinetics as levels decrease.^{8,9,13} Information from previous cases show no brodifacoum induced coagulopathy when serum brodifacoum levels fall below 10 ng/mL and 4 ng/mL. At these levels, discontinuation of vitamin K1 therapy can be trialed.^{5,13,17} It is important to note that coagulation anomalies may persist even if serum brodifacoum levels are undetectable.¹³ Use of phenobarbital has been proposed to enhance brodifacoum hepatic metabolism, but its use has not been shown to improve survival rates or recovery of coagulation factors in brodifacoum poisoning.⁸

Frequent monitoring of a patient's INR is necessary to establish the maintenance dose of vitamin K1.^{3,13} INR should be checked at least every day. If INR is > 2.5 twenty-four hours after the start of vitamin K1, doses should be increased.³ Once INR has been < 2.5 for at least forty-eight hours the patient may be discharged on that dose of vitamin K1. INR should be checked two to three days after the patient is discharged or after any change in vitamin K1 dose.³ Once INR is stable (≤ 1.3), INR check should be repeated every two weeks.^{3,9} If the INR stays stable, consider initiating a slow taper of the vitamin K1 dose with close monitoring of INR every two to three days. If the INR increases but stays < 2.5, maintain the vitamin K1 dose, and if the INR increases > 2.5 return to previous higher dose of vitamin K1.^{3,15} Typically treatment can extend from 3 to 6 months and sometimes more than a year.¹⁵ Patients should be informed of the potential for long term vitamin K1 therapy as this may influence compliance.^{3,7}

Outpatient Considerations

A 2016 report from the Wisconsin Department of Health Services (WDHS) stated that 250,000 citizens of Wisconsin were uninsured in the year of 2016.¹⁸ A substantial issue with synthetic cannabinoid being laced with brodifacoum is the expense of the treatment. Oral therapy of vitamin K1 100 – 200 mg per day may need to be continued for many months.¹⁹ To battle costs of treatment in Illinois, free supplies of vitamin K1 was given with

valid prescriptions until treatment was completed.¹¹

Pharmacists should determine if patients have valid prescription insurance that will pay for the entire treatment course needed for vitamin K1 therapy prior to discharge. It is recommended that patients covered by state Medicaid insurance plans have all prior authorizations recorded before discharge and/or patients eligible should be enrolled in the their particular state's Medicaid program before leaving the hospital to ensure coverage.¹⁹ If no insurance coverage is possible, the WDHS recommends checking qualification for the Valeant pharmaceuticals insurance discount program.²⁰ Other available federally qualified health center or hospital medication assistance programs can be employed to help patients continue their vitamin K1 therapy if the patient does not qualify for the Valeant discount program.

It is critical that this therapy goes uninterrupted and patients are educated on proper medication refilling procedures. Treatment for hypercoagulopathy caused by brodifacoum may last for up to a year or longer.⁷ Therefore, it remains critical to educate at every refill about the signs and symptoms of bleeding: decreased bruising time, blood in the urine or stool, extreme dizziness or fatigue. Additionally, frequent prothrombin time labs are needed to direct the course of vitamin K treatment and not brodifacoum blood concentration alone due to increased bleeding risk even without traces of brodifacoum in the body.⁷ Patients should call their pharmacies five days before their medication runs out to ensure that there is enough vitamin K1 on hand and to order more if needed. Pharmacist should follow up with patients to ensure they are getting their refills as needed due to the risks associated with treatment interruption.⁷ In addition, patients should be advised that over the counter (OTC) dietary supplements containing vitamin K1 only contain 100 mcg (0.1 mg) and are not an effective treatment for this coagulopathy.¹¹

One of the causes for synthetic cannabinoid/brodifacoum poisoning is suicide attempt.^{2,3} Patients need to be assessed for suicidal ideation or tendencies prior to discharge so that they can get necessary help. A very easy tool to use for

this is the Colombia - Suicide Severity Rating Scale (C-SSRS) screening.²¹ It has a minimum of three questions identifying thoughts, plans, or attempts of suicide. Knowing how to ask these questions and how to actively assist and arrange to help patients is vital to ensure that patients with brodifacoum toxicity with risks of suicide are properly evaluated and re-exposure is avoided.²¹

Conclusion

Synthetic cannabinoid tainted with brodifacoum poses a significant health risk. Although it appeals to pleasure seekers, it can lead to potentially fatal events when consumed. Patients with suspected or known ingestion should be monitored for signs of bleeding prior to discharge. In patients presenting with unexplained bleeding, brodifacoum toxicity should not be ruled out and immediate strategies to mitigate bleeding should be initiated. Affected patients need long-term vitamin K1 therapy until monitoring parameters are within normal limit. Compliance to the vitamin K1 regimen and follow-up should be emphasized to prevent re-admission or risk of mortality. Pharmacists should work with patients and other healthcare providers to ensure that patients have continuous access to vitamin K1 therapy. In situations where toxicity is as a result of suicidal tendencies, patients involved should be appropriately evaluated and triaged to avoid re-exposure.

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