Superwarfarin Poisoning: Toxicology and Treatment

Destiny Mishler, PharmD
PGY1-Pharmacy Practice Resident
mishler.destiny@mayo.edu

Pharmacy Grand Rounds
November 13th, 2018
Objectives

Discuss the pharmacokinetics of brodifacoum

Given a patient case, select the most appropriate treatment for a brodifacoum-poisoning patient presenting to the emergency department

Identify a treatment plan for brodifacoum-poisoning patients upon discharge from the hospital
Synthetic Cannabinoids

- K2, Spice, Synthetic Marijuana
- >50 individual synthetic mind-altering chemicals
  - Sprayed on dried, shredded plants
  - Liquids
- Similar chemicals to cannabinoids
- Unpredictable effects
- Dangerous and life-threatening

Health Advisory: Significant Bleeding Associated with Contaminated Synthetic Cannabinoids. Minnesota Department of Health: Minnesota Poison Control Center; 2018.

## Synthetic Cannabinoid Exposure

### Symptoms
- Memory loss
- Nausea
- Vomiting
- Anxiety/Panic Attacks
- Tachycardia
- Psychosis

### Severe Toxicity
- Acute kidney injury
- Seizures
- Pulmonary infiltrates
- Death

**Wisconsin Poison Center Synthetic Cannabinoid Guideline. Wisconsin Poison Center. 2018.**

Patient Case

- J.K. is a 65-year-old male presenting to the emergency department with complaints of:
  - Bloody urine
  - Coughing up blood
  - Headache
  - Severe abdominal pain
  - Bloody stools

Patient Case

- Past medical history
  - Hypertension
  - Diabetes
  - Chronic kidney disease
  - Denies recent trauma

- Medications
  - Lisinopril
  - Metformin

- Social History
  - Smokes 1 pack of cigarettes/day
  - Smokes K2 2-3 times/week
    - Last use 2 days prior
  - Negative for alcohol use

Patient Case

Vital Signs
- 37° C
- 144/80 mm Hg
- Respirations: 18
- 98% O₂ sat on room air
- 131 beats/minute

Labs
- Hgb: 13.3 mg/dL
- Plts: 195
- INR: >10
- Scr: 1.2

Computed tomography
- Head-no signs of intracranial hemorrhage
- Chest-pulmonary hemorrhage
**Synthetic Cannabinoids**

- Intentionally adulterated with brodifacoum
  - Thought to extend the duration of euphoria
- As of April 25, 2018 in Illinois:
  - 155 cases
    - 76 confirmed
    - 79 probable
  - 4 deaths (2.6%)
    - 95% hospitalized
    - 81% experienced hematuria
- 38 cases in 8 other states
Background

• 1940: Anticoagulant in sweet clover discovered
• 1948: Warfarin synthesized
  • Wisconsin Alumni Research Foundation
  • Approved as a rodenticide
• 1954: Approval for human use
• 1960: Discovery of rodent populations with inherited resistance to warfarin
• 1975: Brodifacoum developed
Warfarin Mechanism of Action

Inactive Factors 2, 7, 9, & 10

Carboxylase Epoxidase

Vitamin K

Active Factors 2, 7, 9, & 10

Vitamin K epoxide

Warfarin Reductase

Warfarin

Vitamin K epoxide

Active Factors 2, 7, 9, & 10
Brodifacoum Pharmacokinetics

• “Super” rodenticide
  • High lipid solubility
  • Increased affinity for hepatic tissue
  • Saturation of hepatic enzymes at very low concentrations
  • Zero-order elimination at higher concentrations

100-fold greater decrease in vitamin K-dependent coagulation factors
# Brodifacoum Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Brodifacoum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>17-37 hours</td>
<td>16-34 <strong>days</strong></td>
</tr>
<tr>
<td>Duration of Action</td>
<td>Up to 5 days</td>
<td>2-9 <strong>months</strong></td>
</tr>
<tr>
<td>Onset</td>
<td>Within 24 hours</td>
<td>Delayed several days</td>
</tr>
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Lethality of Brodifacoum

- Study in Rats
  - Single-dose LD₅₀ warfarin = 186 mg/kg
  - Single-dose LD₅₀ brodifacoum = 0.26 mg/kg
- Intracranial hemorrhage - most common cause of death

Deng Y, Qiu L. Therapeutic plasma exchange: a second-line treatment for brodifacoum poisoning following an anaphylactoid reaction to vitamin K. Clinical Case Reports. 2017;5(1) 35-38.

Toxicology of Brodifacoum Exposure

- **Severe coagulopathy that can last weeks to months**
  - Symptoms present many days after exposure and include:
    - Bruising
    - Bleeding
  - Most common sites
    - Genitourinary
    - Gastrointestinal

Sources of Exposure

- Inhalation or oral ingestion of brodifacoum-adulterated synthetic cannabinoids
- Oral ingestion of common household rodenticides that contain brodifacoum
Question 1

• Which of the following characteristics of brodifacoum’s pharmacokinetics, results in an increased half-life compared to warfarin?
  a. Low affinity for hepatic tissue
  b. First-order elimination at high concentrations
  c. High lipid solubility
  d. Metabolized by CYP3A4
Treatment of Brodifacoum Poisoning
Considerations

- Regional Poison Control Center
- Time since ingestion
- Estimated dose
- Signs and symptoms of bleed

Small Dose Oral Ingestion

• Common among pediatrics
• Single, small ingestions are often asymptomatic
  • <1 mg of brodifacoum-watch at home
• Activated Charcoal
• Follow-up INR in 48 hours

Activated Charcoal

- Criteria for use
  - Potentially life-threatening ingestion (>1 mg)
  - Normal mentation
  - Significant bleed absent
  - No aspiration risk
  - Two hours or less since ingestion
Activated Charcoal Dosing

• Adult Dose
  • 50 to 100g orally once

• Pediatric Dose
  • <1 year old: 1g/kg
  • 1-12 years: 25 to 50g
  • >12 years: Adult dosing
Coagulopathy Treatment
Elevated INR

- INR <10, no active bleed
  - Oral vitamin K 50 mg twice daily
- INR ≥10, no active bleed
  - Oral vitamin K 50 mg three times daily
- Daily INR and titrate the dose as needed
Major Bleed

- Life-threatening bleeding
- Hemodynamic instability
- Symptomatic bleeding in a critical area or organ
- Bleeding that causes a hemoglobin level to fall 2 g/dL or more, leading to a transfusion of ≥ 2 units of whole blood or red cells

Major Bleed with Elevated INR

1. Four-factor Prothrombin Complex Concentrate OR
2. Fresh Frozen Plasma

• 10 mg IV Vitamin K
• Initiate 50 mg oral vitamin K three times daily
Four-factor Prothrombin Complex Concentrate

- Weight-based dosing between 25-50 units/kg

<table>
<thead>
<tr>
<th>Pretreatment INR</th>
<th>Four-factor PCC dose</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3.9</td>
<td>25 IU of factor IX/kg</td>
<td>2500 IU</td>
</tr>
<tr>
<td>4-6</td>
<td>35 IU of factor IX/kg</td>
<td>3500 IU</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50 IU of factor IX/kg</td>
<td>5000 IU</td>
</tr>
</tbody>
</table>

- May be re-dosed every 12 hours
- Thrombosis risk increases with dose
- Contains heparin
Fresh Frozen Plasma

- If factor replacement not available
- Dose: 15 mL/kg
- Check INR 15 minutes after infusion complete
- Large volume, caution in patients with:
  - Heart Failure
  - Kidney Disease
  - Intracranial Hemorrhage

Phenobarbital

- In a rat model, duration of coagulopathy was decreased by administration of phenobarbital
- Increase hepatic elimination through microsomal activity
- 100-180 mg daily
- Sedation risk


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Question 2

- Select the most appropriate therapy for J.K.
  a) 4-factor Prothrombin Complex Concentrate
  b) Fresh Frozen Plasma with IV vitamin K
  c) IV and oral vitamin K
  d) 4-factor Prothrombin Complex Concentrate with IV vitamin K and oral vitamin K
Oral Vitamin K Management

- INR 24 hours post vitamin K initiation
  - INR > 2.5 increase dose
  - INR ~1 consider decrease in dose
- INR 1 to <2.5 for 48 hours on oral vitamin K, ready for discharge
- Vitamin K supply should be arranged prior to discharge
- 100 mg = 20 tablets daily
  - 30 day supply = $37,000
Ambulatory Treatment
Long-term treatment

• Suggested follow-up with managing provider 2-3 days post hospital discharge, then every 1-2 weeks

• When INR reaches normal, decrease vitamin K
  • Check INR 2-3 days after decrease

• Duration of therapy: 51 days to 9 months
Long-term management strategy

- Goal INR 1.2-1.8
- 40-50 mg twice daily for one month
- Wean the patient by 5 mg twice daily
  - INR 7-14 days later
- If stable, drop by another 5 mg twice daily
- If INR increased, reinstitute prior dose for two weeks, then attempt wean once INR stable again
Question 3

- After 5 days of treatment, J.K. is stable and ready for hospital discharge. Select the best possible discharge plan for the patient.
  a) Vitamin K 10 mg IV once daily for 7 days
  b) Vitamin K 100 mg PO three times daily for 1 year
  c) Vitamin K 50 mg PO three times daily for 4 weeks with follow-up 2 days after discharge
  d) Vitamin K 50 mg by mouth once daily for 4 weeks with follow-up 2 weeks after discharge
Summary

• Brodifacoum’s lipophilicity and increased hepatic affinity results in increased potency and half-life compared to warfarin

• Life-threatening bleed due to brodifacoum poisoning is treated with 4-factor prothrombin complex concentrate, fresh frozen plasma, and vitamin K

• Outpatient treatment of brodifacoum poisoning may include high doses and extended durations of oral vitamin K
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18. Ng WY, Ching CK, Chong YK. Retrospective Study of the Characteristics of Anticoagulant-Type Rodenticide Poisoning in Hong Kong. Journal of Medical Toxicology. 2017;14:218-228.

