RECURRENT COAGULOPATHY AFTER CROTALINE ENVENOMATION

by Michael Rognon, PharmD

Case
A 49-year-old female was bitten on the ankle by a rattlesnake while hiking. She went immediately to the hospital where she presented with pain, swelling, redness, and bruising that progressed to her mid-thigh. During hospitalization, her platelet count dropped to 63,000/mm$^3$. She received a total of 30 vials of antivenom (Crotalinae polyvalent immune Fab) and was discharged on hospital day 3 following improvement of local symptoms and resolution of coagulopathy. At a follow-up visit 8 days after envenomation, her platelet count was 16,900/mm$^3$. She received 4 additional vials of antivenom, and her platelets rebounded to 37,000 the next day. She was subsequently monitored on an outpatient basis every 2-3 days. Her platelet count continued to trend upward and reached 94,000/mm$^3$ on day 15 after envenomation. She experienced continual improvement, thereafter.

Introduction
The majority of venomous snakes in the U.S. belong to the crotaline family. Although fatal outcomes after crotaline envenomation are rare, significant morbidly is of concern. Patients can present with the initial signs and symptoms of snake envenomation, but can also develop delayed complications that must be monitored carefully and may require treatment. The purpose of this discussion is to examine the presentation and treatment of crotaline snakebites, with an emphasis on recurrent coagulopathy after envenomation.

Crotaline Envenomation
Members of the crotaline family include rattlesnake, massasaugas, copperheads, and cottonmouths. Not all bites from these snakes result in envenomation, but can also develop delayed complications that must be monitored carefully and may require treatment. The purpose of this discussion is to examine the presentation and treatment of crotaline snakebites, with an emphasis on recurrent coagulopathy after envenomation.

Table 1: Hemostatic Characteristics of Snake Venom

| 1. Enzymes that clot fibrinogen |
| 2. Enzymes that degrade |
| 3. Plasminogen activators |
| 4. Prothrombin activators |
| 5. Factor V activators |
| 6. Factor X activators |
| 7. Anticoagulant activities fibrinogen |
| 8. Enzymes with hemorrhagic activities |
| 9. Enzymes that degrade plasma serine proteinase inhibitors |
| 10. Platelet aggregation inducers |
| 11. Platelet aggregation inhibitors |

Treatment
Pre-hospital management of a snake bite includes immobilizing the extremity, removing potentially constricting (cont. on pg. 2)
HOME DRUG TESTING
Elyse MacDonald, PharmD

There are numerous types of home medical testing kits available for purchase at retail pharmacies and internet websites. These tests include pregnancy, drug screens, and glucose monitoring, to name a few. Some FDA devices undergo a premarket approval process whereas other devices are only required to undergo a premarket notification and clearance process. Home drug testing kits fall under the premarket notification and clearance category. Companies submit a premarket notification (510k) to the FDA who “clears” the product if it is determined to be substantially equivalent to a legally marketed product. FDA cleared the first home drug testing kit in 1997, and within the next year, more than 200 home drug tests were available for purchase.1

Multiple types of drug tests are available. Some devices screen for several drugs or drug categories such as opiates, cocaine, marijuana, amphetamines, and methamphetamines whereas other devices may be marketed for a single drug or drug category. When purchasing a drug test, it is important to ensure the product was cleared by the FDA.2 The FDA suggests that the consumer ask the seller for the FDA clearance number. In order to verify the clearance number, call the FDA’s Division of Small Manufacturers, International and Consumer Assistance at 1-888-463-6332. Additionally, the FDA suggests reading the labels on the testing kits. Labeling in multiple languages or metric units of measures indicate the product may have originated outside of the United States and may not have been cleared by the FDA.

As with any test, there is a chance for false-positive or false-negative results. False-positives may occur due to cross-reactivity of other medications with agents in the test.1,3 For example, pseudoephedrine may give a false-positive for amphetamines.3 Positive results from home drug testing kits do not confirm an individual is abusing drugs.1 Negative results from home drug testing kits do not confirm the individual does not take part in drug use. Reasons for negative results include the individual does not use drugs, dilute concentration of drug being analyzed, or no recent drug use so the drug is no longer detectable.1 Laboratory tests are required to confirm a positive or negative result. Some home drug testing kits allow the consumer to send in the sample for confirmation analysis for an additional fee.

The American Academy of Pediatrics (AAP) does not support drug testing of adolescents without their consent. The AAP encourages parents to consult the child’s pediatrician rather than rely on home drug-testing products.4

In conclusion, home drug testing kits are readily available to the public. Clinicians may be consulted about interpretation of home drug testing kits. The same issues discussed with toxicology screening (Toxicology Today Vol. 11 Issue 3) exist with home drug testing kits; with the additional challenge that they may not have been “cleared” by the FDA. Home testing kits cannot confirm a positive or negative result and laboratory testing should be conducted for confirmation of home testing kit results.

References

(Cont. from pg. 1)

Recurrent Coagulopathy
jewelry and transport to the nearest hospital. The mainstay of hospital treatment is supportive care and administration of antivenom. Antivenom is most beneficial if given within 6 hours of envenomation, but has been shown to be effective in one patient 52 hours after envenomation.1 Patients should be monitored for progression of swelling by tracking edge of edema with a pen every 15-30 minutes. Patients receiving antivenom should be initially monitored in the ED or ICU, due to the possibility of anaphylactic reaction.

Antivenom treatment was previously initiated with Antivenin Crotales Polyvalent (ACP), an equine derived product. This antivenom is no longer manufactured and has been replaced with the newer Crotaline polyvalent immune Fab (FabAV/CroFab®), an ovine product that has a lower risk for anaphylaxis but a shorter half-life. Laboratory monitoring should include a complete blood count, platelets and coagulation studies including INR, aPTT, and fibrinogen. Most patients who receive antivenom require observation for at least 24 hours and may be discharged after the swelling begins to decrease and any coagulopathy has resolved.1,8

Recurrent Coagulopathy
A recurrent coagulopathy is an abnormality of coagulation that returns after an initial coagulopathy has resolved. The coagulopathy can involve a single abnormal finding, or a combination of abnormal findings. Several possible mechanisms may be at work in causing a recurrent coagulopathy after crotaline envenomation. Suggested mechanisms include a depot of unneutralized venom at the bite site, reversible binding of antivenom, late onset components of the venom, host antivenom response, and a difference in pharmacokinetics/dynamics between the venom and antivenom and the shorter half-life of FabAV.9 The true incidence of recurrent coagulopathy is not known. In a multicenter clinical trial of FabAV 29/38 (76%) of patients developed a coagulopathy with the coagulopathy described as late, persistent or recurrent in 20/29 patients.2 In a retrospective case series of snake bites to (cont. on pg. 3)
Recurrent Coagulopathy

a regional poison control center, 45% of patients were noted to have a recurrence of coagulopathy. In both studies, coagulopathic recurrence generally occurred within the first few days but was delayed up to 2 weeks. The risk of recurrence is higher if hematologic abnormalities are present within the first 36 hours of envenomation. Spontaneous bleeding is rare, but has been reported. Significant bleeding can also arise in patients who undergo surgery or experience trauma soon after envenomation, or have an underlying condition that increases risk of bleeding.

There is no standard treatment for recurrent coagulopathy after crotaline envenomation. Patients have recovered spontaneously with no intervention, while others have required repeat antivenom administration to achieve recovery. While there are no specific guidelines on when to administer additional antivenom for a recurrent coagulopathy, Table 2 provides some general guidance. Patients with recurrent coagulopathy, regardless of whether they receive additional antivenom, should be admitted. The endpoint of treatment is patient improvement and laboratory signs of coagulopathy trending normal.

All patients envenomated by a crotaline snake are at risk for developing a late coagulopathy. While those at greatest risk are patients who experience an early coagulopathy, all patients should be re-evaluated for potential recurrence or late onset of coagulopathy. Patients discharged following crotaline envenomation should be counseled to watch for bleeding. Special care should be taken in patients who undergo surgery, perform high risk activities, or have medical conditions that could increase risk for bleeding.

Summary

Victims of a crotaline envenomation may experience local injury and systemic effects, including coagulopathy. Antivenom is an effective treatment. However, coagulopathies may recur in up to one-half of patients treated with FabAV. Recurrent or delayed coagulopathy can be treated with antivenom. Patients should be monitored frequently until an improvement of symptoms and laboratory values trend towards normal.

Table 2: When to consider repeat antivenom

| 1. Severe coagulopathy – fibrinogen <50 mcg/ml, platelets <25,000/mm³, INR >3, or aPTT >50 seconds |
| 2. Multi-component coagulopathy with abnormalities to a lesser degree |
| 3. A clear worsening trend in patients with severe early coagulopathy |
| 4. Patients with high risk behavior that could result in trauma or co-morbid conditions that could increase bleeding risk |

References

• The FDA added a warning of suicide risk to the label of tramadol. It should not be prescribed to patients who are suicidal or addiction prone.
• High dose, long-term use of proton pump inhibitors (e.g., omeprazole, pantoprazole) has been associated with increased risk of fractures.
• OTC CaNa2EDTA oral tablets and rectal suppositories are being marketed for “chelation therapy” on the internet for conditions such as autism and heart disease. These products are not approved by the FDA. CaNa2EDTA can have liver and kidney toxicity.

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