Snakebite! Crotalinae Envenomation of a Man in Rhode Island

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ABSTRACT

The incidence of poisonous snakebites has regional variance. Health care providers' knowledge and comfort in treating these envenomated patients depends on the density of poisonous snakes in their environment, with practitioners in the southern U.S. typically treating more exposed patients than those in colder regions in the North. We present a rare case of a confirmed copperhead snakebite that occurred in Rhode Island. We will review Copperhead bites, clinical management and treatment options.

KEYWORDS: Agkistrodon contortrix, Crotalinae, antivenin, CroFab, FabAV, Rhode Island

INTRODUCTION

The Copperhead snake (*Agkistrodon contortrix*) is a member of the poisonous Crotalinae (pit viper) subfamily that is indigenous to North America's Southeast and Midwest regions, with most of the reported bites occurring in these areas. According to the American Association of Poison Control Centers (AAPCC), 3,823 crotaline snake exposures were reported in 2013; 47% from copperheads, 30% from rattlesnakes, 7% from cottonmouths, and 15% from unknown crotalines. One hundred and fifty-six of these patients had life-threatening envenomations; 3 deaths were reported.[1] Since this occurs so rarely in the Northeast United States, physicians and health care systems may be less familiar with management, expectations and treatment of poisonous snakebites.

This paper reviews the management of poisonous snakebites, illustrated by a confirmed case of a copperhead snakebite in Rhode Island.

CASE REPORT

Presentation

A 62-year-old man presented to the emergency department (ED) with pain and swelling of his left hand after being bitten by a snake on his left thumb just prior to arrival. 911 was called and an environmental police officer was dispatched from the RI Department of Environmental Management to the scene and identified the snake as a Copperhead (**Figure 1**). The patient reported acute onset of severe pain associated with swelling and numbness that had been progressively worsening since the injury. The patient denied any associated shortness of breath or active bleeding.

Figure 1. Copperhead snake

Physical examination

His initial vitals revealed a blood pressure of 122/76 mmHg, pulse of 76 beats per minute, and temperature of 101.7°F. His respiratory rate was 16 breaths/min, and his oxygen saturation was 100% on room air. He was awake and alert, complaining of pain. His physical examination was normal with the exception of marked swelling and erythema extending from the proximal left thumb to the distal forearm. Two puncture wounds were visible on the volar aspect of the left thumb.

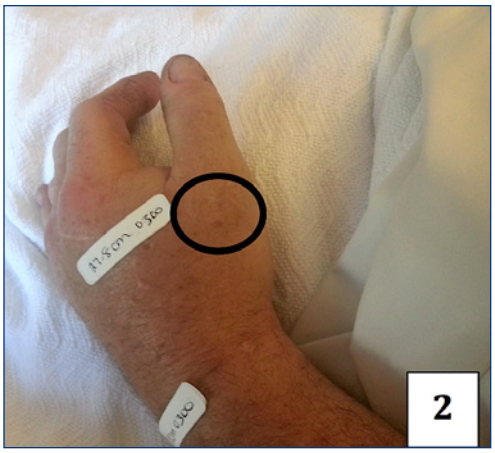
ED management

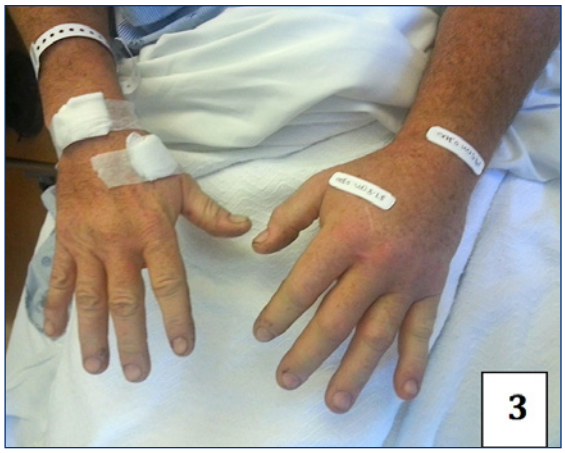
Initial laboratory testing in the ED included PT, aPTT, INR, fibrinogen, D-dimer, lactic acid, platelets and creatinine kinase; all were within normal limits.

In the ED, the patient experienced progressive worsening of pain and swelling extending to his proximal forearm. The Regional Poison Control Center (1-800-222-1222) was contacted and agreed that, because of the severity of his symptoms and rapid progression of swelling proximally, he met criteria for moderate envenomation and recommended administration of FabAV. Four vials of CroFab® were administered in the emergency department and the patient was admitted to the internal medicine service for further observation.

Hospital course

The patient's symptoms improved throughout his 4-day inpatient hospitalization. During that time, he was followed by the Regional Poison Control Center and Plastic and Reconstructive Surgery (PRS) service. He was monitored closely for evidence of coagulopathy, hemolysis, rhabdomyolysis, and shock. His blood work remained normal throughout his hospitalization. Swelling was closely monitored with serial measurements of the left arm (**Figures 2, 3**). The patient received 2 vials of FabAV every 6 hours for 2 additional doses; a 3rd dose was held after discussion with





Figures 2 and 3.
(2) Copperhead bite on left hand, 6 hours after initial Crofab®. Two small puncture wounds can be seen on the dorsal aspect of the left thumb, circled. (3) Comparison of swelling between the two hands.

the Poison Control Center due to improving physical exam and normal blood testing. The patient demonstrated daily improvement in hand swelling and pain control and was discharged on hospital day 4 with minimal swelling on the dorsal and volar aspects of the thumb base, improved erythematous changes, and intact neurovascular functioning of the affected hand. The patient was discharged with a 5-day course of amoxicillin/clavulanic acid for the puncture wound, and follow-up was scheduled with the PRS team.

DISCUSSION

Copperhead Envenomation

Copperhead envenomation is considered less injurious than the other viperidae snakes, with toxic effects including severe pain, local tissue damage and, infrequently, coagulopathy, rhabdomyolysis, neurotoxicity and shock.[2] In a retrospective chart review of 106 confirmed and probable copperhead snakebites among pediatric patients in a tertiary care hospital in St. Louis, Missouri, only five patients had two coagulation laboratory values outside normal ranges. None of the patients developed bleeding complications.[3] Treatment is often supportive care and pain control; however, Crotalinae ovine immune Fab (FabAV), such as CroFab®, may be indicated for moderate to severe envenomation or airway compromise from local tissue swelling (**Table 1**).

Snakebite complications

Classically, compartment syndrome causes severe pain due to tense edema from swollen muscle compartments, often requiring fasciotomy to release the at-risk musculature and neurovascular bundle. In contrast, tissue swelling from snake envenomation is typically caused by subcutaneous edema, as venom migrates primarily in the subcutaneous tissues via the lymphatic system – external to the muscular compartments. In a randomized study of snake envenomation in rabbits, superior survival and muscle function were noted among those treated with antivenin as opposed to debridement or fasciotomy.[4] In 2013, a consensus-based treatment guideline recommended antivenin as the first line treatment, as it reduces compartment pressures and obviates the need for fasciotomy, and recommended against prophylactic excision of the affected tissue since it has not been shown to improve outcomes. Fasciotomy in snakebites is reserved for patients who fail to improve with antivenin or have confirmed increased compartment pressures.[5]

Medical management of snakebites

The affected extremity should be placed on a pillow at a neutral height; significant elevation is not recommended and worsens toxicity by hastening proximal distribution of venom.

Table 1. Symptoms of crotalinae envenomation. Crotalinae ovine immune Fab (FabAV) is indicated for moderate to severe symptoms. FabAV may be considered for mild symptoms, depending on the clinical scenario.

	Mild	Moderate	Severe
Local tissues	Localized swelling and pain at the bite site	Local swelling at the bite site and proximal surrounding tissues Swelling and pain less than 50% entire extremity Swelling less than 50cm on head, neck or trunk	Swelling and pain including entire limb Swelling greater than 50cm on head, neck or trunk Signs of compartment syndrome
Systemic effects	N/A	Nausea, vomiting, diarrhea, tachycardia, tachypnea	Hypotension/shock Severe tachycardia, respiratory failure, altered mental status
Laboratory abnormality	N/A	Abnormal coagulation parameters (i.e. PT, PTT, fibrinogen)	Abnormal coagulation parameters (i.e. PT, PTT, fibrinogen) with serious bleeding

Any potential restrictive accessories, such as rings and watches should be removed. The wound should be carefully washed to remove venom on the skin and tetanus immunization should be given if patient is out of date. Providers should monitor progression of proximal swelling closely by drawing lines at the most proximal edges; the circumference of the affected extremity should be measured and documented every 15-30 minutes. An IV should be placed on a non-affected extremity for medications and fluid. Opioid medication can be used for pain control; non-steroidal anti-inflammatories (NSAIDs) should be avoided as platelet function may already be impaired. Constrictive bandages, tourniquets, or prophylactic antibiotics are not recommended. Furthermore, there is no role for incising the puncture wound and attempting to suck out the venom.

History of antivenin

The original snake antivenin, Antivenin Crotalidae Polyvalent (ACP), was introduced in 1953 and significantly decreased the mortality from snakebites in the United States from 5-36% to less than 1% by the 1960s.[6-8] Its safety profile was unfavorable, however, with a significant incidence of anaphylaxis and serum sickness.

What is FabAV?

Crotalidae Polyvalent Immune Fab (fragment of antibody) antivenins were approved by the FDA in 2000 and are commercially available in the United States as antidotes for indigenous North American viper envenomation. The most widely available FabAV in the U.S. is Crofab®.

The antivenin is derived from sheep immunoglobulin (IgG) and targets the venom of four snakes: Western and Eastern diamondback rattlesnakes, Mojave rattlesnake, and Cottonmouth (Water Moccasin). FabAV binds and neutralizes venom toxins, which allows for their elimination. The antivenin has also demonstrated cross-protection in murine models against: *C. atrox, C. adamanteus, C. scutulatus, A. piscivorus, C. h. atricaudatus, A. c. contortrix, S. m. barbouri, C. h. horridus*.[9] FabAV may also be beneficial against some Middle Eastern and North African snakes, although clinical data is lacking.[10]

How does FabAV work?

FabAV is efficacious in controlling the toxicity of Crotalidae bites in patients with minimal to moderate envenomation,[1, 11-17] and improves patient outcomes in severe envenomations by halting coagulopathy and limiting systemic toxicity.[18]

Who requires FabAV?

Indications for initiation of FabAV include most bites with more than minimal swelling, systemic symptoms or with any laboratory abnormality: swelling that is progressively worsening, elevated prothrombin time (PT), decreased fibrinogen or platelets, or any systemic involvement, including altered mental status, hypotension, tachycardia or tachypnea. Please refer to Table for additional moderate to severe symptoms requiring FabAV. Dry bites, as evidenced by the presence of fang or tooth marks without evidence of envenomation (i.e. no swelling, minimal pain, no systemic symptoms), occur in up to 25% of Crotaline bites. Dry bites do not require treatment with FabAV and patients may be discharged home after at least 8 hours of observation without changes in their clinical status or abnormal labs prior to discharge.

What is the FabAV loading dose?

Patients with mild to moderate symptoms (Table) initially require 4 to 6 vials (approximately 4 to 6 g) of reconstituted FabAV. A second dose of 4 to 6 vials may be warranted if initial control is not obtained within one hour of treatment.[19] Initial control is defined as arrest of progression of swelling, reversal of coagulation abnormalities, and overall improvement in clinical condition.

In patients with severe envenomation, higher doses of FabAV may be required to achieve initial control. In one study, patients with severe envenomation required a median dose of 9 vials to stop proximal progression of swelling and systemic symptoms and 25% of patients required more than 15 vials.[18] Of the confirmed snakebites in the study, rattlesnake bites resulted in 13% of severe envenomations, while copperhead bites did not result in any severe systemic effects.[18]

Pediatric patients require the same dose of FabAV as adults, as the severity of envenomation depends primarily upon dose of venom injected, not on the size of the victim.

How is FabAV administered?

FabAV must be reconstituted carefully with a swirling or twisting of the vials and not shaking. The induction of bubbles with shaking renders the antidote unusable. FabAV is most effective when infused within 6 hours of envenomation, although repeat administrations may be required due to the shorter half-life of FabAV in comparison to Crotalinae venom.[1] In order to prevent rebound toxicity in patients with moderate to severe envenomation, it is recommended that these patients receive a scheduled dose of 2 vials of FabAV every 6 hours for 3 doses.

FabAV complications

FabAV has a much lower incidence of severe hypersensitivity reactions and serum sicknesses than its predecessor ACP. Nevertheless the initial infusion should be administered in an emergency or intensive care unit setting. The estimated immediate and delayed hypersensitivity following FabAV administration is 6% and 8%, respectively.[20] Patients with known ovine or papaya allergies should be pretreated with intravenous diphenhydramine and methylprednisolone, and epinephrine should be immediately available in case of anaphylaxis.

The most common side effect is a rate-related anaphylactoid reaction. In this circumstance, the infusion should be temporarily stopped and the patient's symptoms addressed.

It can then be restarted at a slower rate.

Serum sickness presents days after administration with joint pain and swelling and is often non-fatal; it is generally treated with a course of systemic steroids.

Severe acute hypersensitivity symptoms include anaphylaxis. Patients with anaphylaxis should receive appropriate medical treatment. Antivenin administration should be stopped and should not be restarted.

In a multicenter observational case series of 209 patients immediate hypersensitivity reactions and serum sickness were reported in 6.1% and 5% of patients, respectively.[18] Four patients experienced serious immediate hypersensitivity reactions, and one patient required cricothyroidotomy.[21] Overall, there is risk associated with FabAV administration, but it is rare and should not prevent administration of this critical antidote to patients in need.

Disposition of snakebite patients

Patients receiving FabAV should be admitted to the hospital for observation. Patients discharged home should be instructed to monitor for worsening swelling or abnormal bleeding. Patients who did not receive FabAV do not need follow-up appointments.[22]

FUTURE DIRECTIONS

In addition to the ovine-derived FabAV, an equine-based, F(ab')2 antivenin, Anavip®, has been approved by the FDA but will not be commercially available in the United States until 2018 or 2019. Anavip is derived from Bothrops asper and Crotalus simus immunizing venoms and has been shown in phase 3 clinical trials to have a longer half-life than CroFab. Furthermore, data suggests a lower frequency of late coagulopathy after Anavip administration when compared to CroFab (5–10% versus 30%), and a similarly low rate of acute serum reaction and serum sickness in both groups.[1, 19]

CONCLUSION

The initial management of Crotaline envenomation should be coordinated with the national Poison Control center and, if available, local toxicology consultants; the decision to administer FabAV should be based on symptom severity.

Wound care and diagnostic testing are essential in determining severity of the envenomation. Tracking and marking the progression of edema assists in grading symptoms and assessing response to therapy. Appropriate limb placement and prompt removal of potentially constricting items are critical steps in reducing complications. Serology should be directed for development of coagulopathy, hemolysis and myonecrosis to identify an envenomation that requires antivenin administration.

Antivenin administration should be given quickly for those patients with moderate to severe symptoms, and may be considered in the setting of mild symptoms. The currently recommended FabAV infusion is rarely associated with severe acute hypersensitivity reactions. Halting the progression of local symptoms and reversing any systemic effects will guide the dosing and administration of reconstituted FabAV over the course of clinical observation.

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