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Pit Viper Envenomation In Dogs: Pathophysiology and Treatment

DAVID SENTER, DVM\textsuperscript{1}, AND TOM CARSON, DVM, PH.D.\textsuperscript{2}

Copperhead (Agkistrodon contortix). This species enjoys widespread distribution across the U.S., ranging from Texas and Oklahoma in the southwest, Iowa to the northwest, New York and Massachusetts to the northeast, and Florida to the southeast. This species is among the most commonly encountered pit vipers in the U.S., however it is also among the least dangerous in terms of venom toxicity and volume of injection.

Venomous snakes occur throughout a very wide geographic area within the United States. In certain areas of the country, snakebites in dogs are diagnosed on a regular basis during the warm months of the year when snakes are most active and people and their pets are most likely to be spending time in areas that snakes inhabit. The best treatment for snakebite is a controversial subject among veterinarians and there is no single treatment protocol. Therefore, it is necessary for a clinician to understand the pathophysiology behind envenomation in order to make educated decisions as to the treatment of each individual patient.

An estimated 15,000 domestic animals are bitten by snakes annually in the United States. Approximately 80% of fatal bites are inflicted by rattlesnakes.\textsuperscript{1} Members of the Crotalidae (pit viper) family account for the large majority (95%) of poisonous snakebites. The three main genera in this family are Crotalus (rattlesnake), Agkistrodon (copperhead, cottonmouth water moccasin), and Sistrurus (pygmy rattler, massasauga).\textsuperscript{2} Among these groups, there are at least 26 subspecies of rattlesnakes, five subspecies of copperheads, three subspecies of cottonmouths, three subspecies of pygmy rattlesnakes, and three subspecies of massasauga.\textsuperscript{1} Members of the pit viper family get their name from the facial pits that exist between the nostril and the eye which function to detect heat and vibration.\textsuperscript{1,2} Other distinguishing characteristics of the crotalids include triangular shaped heads, retractable fangs, a single row of subcaudal scales, and vertical, elliptical shaped pupils. All pit vipers have movable fangs that inject a voluntarily controlled amount of venom.\textsuperscript{2}

Pathophysiology

In general, pit viper venom is considered hemotoxic and proteolytic as opposed to many snakes that are predominately neurotoxic.\textsuperscript{3} The Mojave green rattlesnake (Crotalus scutulatus scutulatus) is an exception as its venom contains a very substantial quantity of neurotoxin. Venom constituents vary considerably between snakes of different species as well as between individuals within a species depending on geographic location, age, and season of the year.

Of the three genera in the pit viper family, the rattlesnakes have the most potent venom with the eastern and western diamondback rattlesnakes accounting for 95% of fatalities in man.\textsuperscript{2} The relative toxicity of venom from several North American snakes are listed in Table 1.

Snake venom consists of a diverse mixture of peptides, enzymes, and proteins. At least 26 different enzymes have been defined, ten of these are common to all pit viper venoms. One major enzyme is hyaluronidase which allows the venom to spread and pen-
Table 1. Venom Toxicity of Some North American Snakes

<table>
<thead>
<tr>
<th>Snake</th>
<th>LD50 mg/kg⁻¹ 1987</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rattlesnakes (Crotalus)</td>
<td></td>
</tr>
<tr>
<td>Mojave (C. scutulatus scutulatus)</td>
<td>0.23</td>
</tr>
<tr>
<td>Eastern diamondback (C. adamanteus)</td>
<td>1.68</td>
</tr>
<tr>
<td>Western diamondback (C. atrox)</td>
<td>2.18</td>
</tr>
<tr>
<td>Timber (C. horridus horridus)</td>
<td>2.69</td>
</tr>
<tr>
<td>Pygmy rattlesnakes (Sistrurus)</td>
<td></td>
</tr>
<tr>
<td>Pygmy (S. miliaris)</td>
<td>2.85</td>
</tr>
<tr>
<td>Massassauga (S. catenatus)</td>
<td>2.91</td>
</tr>
<tr>
<td>Moccasins (Agkistrodon)</td>
<td></td>
</tr>
<tr>
<td>Cottonmouth (A. piscivorus)</td>
<td>4.19</td>
</tr>
<tr>
<td>Copperhead (A. contortrix)</td>
<td>10.92</td>
</tr>
</tbody>
</table>

LD50 values are from a study which administered venom intravenously in 18 to 26 gm mice.

traitate tissues by decreasing the viscosity of connective tissue.⁴ Another major component is phospholipase A₂ which disrupts cell membranes, uncouples phosphorylation, inhibits cellular respiration, and may release histamines, kinins, and serotonin. Phospholipase A₂ acts by liberating arachidonic acid from membrane phospholipids which is then converted to various prostaglandins (PGI₂, PGE₂, PGF₂α) and thromboxane A₂.³ Prostaglandin E₂ and PGI₂ cause vasodilation and decrease systemic arterial pressure that contributing to hypotension. Another component, thromboxane A₂, is a potent inducer of platelet aggregation which may contribute to thrombocytopenia. Several attempts to measure the amount of histamine released after contact with snake venom have been performed by various in vitro tests with mixed results. However, no in vivo direct test of the histamine-releasing activity of Crotalus species venom has been reported.³ The nonenzymatic polypeptide component of Crotalidae venom has more of a direct effect on the cardiovascular and respiratory system.

Cardiovascular System

A lethal factor in Crotalus species venom disrupts the basal lamina and collagen of the capillaries allowing for leakage of red blood cells and plasma through the endothelial membrane.¹³ Petechia, ecchymosis, and extensive edema are commonly seen due to the vascular destruction and increased vascular permeability. Approximately one-third of the total circulating fluid volume can be lost into an affected extremity within hours of envenomation.¹³ Furthermore, severe hypotension commonly occurs due to pooling of blood in the hepatosplanchnic bed in dogs.³ This combination can ultimately lead to hemoconcentration, lactic acidosis, and hypovolemic shock.

Some envenomated patients will have concurrent thrombocytopenia which may be due to the aggregation of platelets to areas of damaged endothelium and the production of thromboxane A₂ and PGE₂ from phospholipase A₂. Venoms from several species of rattlesnake have been shown to cause significant decreases in platelet counts in vitro.⁵
Mojave rattlesnake, Mojave Green rattlesnake (Crotalus scutulatus). Mojave rattlers are unique among rattlesnake species in that their venom contains a significant neurotoxic component. Per volume, this venom is the most highly toxic of all the North American pit vipers. This species ranges from southwest Utah to southern Nevada and the Mojave Desert region and southward to central Mexico.

In general, snake venom has very complex effects on blood coagulation. Many of the rattlesnake venoms studied cause the formation of an imperfect fibrin clot which results in pure defibrination and high levels of fibrin degradation products. This cause is differentiated from disseminated intravascular coagulation (DIC) by the fact that platelets and factor VIII are not consumed. Unlike with DIC, this condition is not inhibited by heparin. Cottonmouth and copperhead venom affects coagulation in a different manner. Since their venoms interfere with the formation of fibrin, defibrination does not occur. However, these do cause hypofibrinogenemia from the dissolution of fibrinogen. Many venoms have procoagulant properties and anticoagulant properties. Nevertheless, the overall effect of most severe pit viper envenomations is an anticoagulative state.

Nervous System

The Mojave rattlesnake is the only member of Crotalidae found in North America whose venom has a significant neurotoxic component. This toxin (Mojave toxin) interferes with neuromuscular transmission by a presynaptic nerve-blocking action. The major toxic effects involve the peripheral nervous system and include respiratory paralysis and general flaccid paralysis. However, its greatest effect is on motor axon terminals of the diaphragm and respiratory paralysis may not occur for several hours after envenomation.

Urinary System

Most pit viper venoms, especially those of the western diamondback rattlesnake and the prairie rattlesnake, cause myonecrosis which could cause the release of myoglobin. Therefore, if severe envenomation has occurred, the nephrotoxic effects of myoglobinuria may result in acute renal failure. Other potential nephrotoxic factors include hemoglobinuria (some venoms cause intravascular hemolysis), defibrination syndrome, and hypovolemic shock.

Clinical Signs and Diagnosis

Snake envenomation can be difficult to diagnose if the incident was not witnessed. Clinical signs may vary greatly depending on the species of snake involved and the quantity and toxicity of the venom injected. The potency of the venom depends on several factors such as age of the snake (young snakes have high peptide fractions), the volume of venom regenerated since the last bite, aggressiveness of the snake, and motivation of the snake (offensive strikes are usually more severe). In addition, the enzymatic fraction of the venom is higher in the fall and lower in the spring in relation to the peptide fraction.

Most bites in dogs involve the head, face, or neck. Bites to the body rarely occur, but tend to involve much more severe envenomation. Dogs commonly present with extensive edematous swelling, severe pain, ecchymosis, and discoloration of the skin in the affected area within several hours after the bite. It is advisable to clip the hair in the area to search for fang marks (one or more with multiple strikes). Bleeding puncture wounds may indicate the bite of a pit viper. If fang puncture wounds are present in the absence of pain and swelling, the dog may have received a dry or nonpoisonous bite. It is estimated that poisonous snakes fail to inject venom in up to 20% of bites. However, some bites by the Mojave rattlesnake may be life-threatening without pain or swelling. All patients should be hospitalized and monitored for at least 24
hours for signs of systemic envenomation. Some laboratories can perform blood analysis to determine the concentration and type of venom injected, however, this method is not routinely used in North America.6,7,8

Systemic signs can vary and may include hypotension, shock, cardiac arrhythmias, bleeding disorders, ptyalism, nausea, vomiting, respiratory distress, mental confusion, rhabdomyolysis, and acute renal failure.1,2,6 A

baseline of laboratory data should be obtained upon presentation including: complete blood count, platelets, coagulation profile (prothrombin time, partial thromboplastin time, fibrinogen), serum electrolytes, blood urea nitrogen, creatinine, creatine phosphokinase (CPK), glucose, and urinalysis.1 If severe envenomation is suspected, electrocardiographic monitoring should be performed.

Wright-Giemsa stained blood smears should be evaluated in all suspected cases of snakebite. A study of 28 cases of rattlesnake bites in dogs indicated an association of envenomation with echinocytosis; 25/28 dogs (89%) had echinocytosis within 24 hours after the bite.9 Since slow drying of blood films can cause the artificial formation of echinocytes (crenation), a saline wet mount preparation should be made of both the suspected victim and a healthy, nonenvenomated dog for comparison. This prep can be done by mixing a drop of isotonic saline with one drop of EDTA-preserved blood on the slide. A cover slip is added and the sample observed with a light microscope. The echinocytosis is a transient shape change with most cases resolving by 48 hours.

The aforementioned study also reported that sixty-four percent of dogs bitten by rattlesnakes developed thrombocytopenia, 10 of 28 (36%) dogs had mild anemia, and 14 of 18 (78%) developed hypokalemia.9 Anemia may be due to cell destruction following envenomation. The cause of the hypokalemia was not apparent, however, it does indicate the need for supplementation during treatment. On the contrary, hyperkalemia can commonly be seen in severe envenomations that cause extensive necrosis, hemolysis, and oliguric renal failure. If severe rhabdomyolysis has occurred, CPK levels will be markedly elevated within the first 12 hours post-envenomation.1 Urine should be analyzed for myoglobinuria and hemoglobinuria and renal function should be closely monitored for signs of renal failure.

### Treatment

**Pre-hospital.** The treatment for snakebites in both humans and animals is surrounded by much folklore and anecdotal evidence of successful treatments. Even within the scientific literature, there is much controversy regarding the most successful treatment protocols in these patients. The treatment the animal receives before it gets to the hospital can be important in the outcome of these cases. The most important recommendation for clients is to strictly limit the physical activity of the dog. The venom is spread through the lymphatics and excessive activity will increase the uptake of the venom.4 If an extremity is bitten, immobilization of the leg with a splint may be helpful if this can be rapidly performed.2 Noting the levels of swelling every 15 minutes during transport may help to determine the degree of envenomation. It is not advisable to use a tourniquet to stop the spread of venom, pack the area in ice, or incise the wound for suction. These practices have not proven useful and may cause further injury.2 Recently the popular press has described electric shock therapy for treatment of poisonous snakebites. Scientific investiga-
tion of this technique indicates that it is of no value and may actually be harmful to the animal. Transporting the dog as quickly as possible to the nearest veterinary medical facility is the most prudent course of action to take.

**Initial.** Some patients may present in respiratory distress after envenomation by the Mojave rattlesnake or due to swelling around the upper airways. Emergency tracheotomy may be indicated in patients with extensive swelling in the neck area. After the airway is secured, intravenous fluid therapy is appropriate to support blood pressure and perfusion. Since cardiovascular collapse due to hypovolemic shock is the primary cause of death, aggressive fluid therapy is indicated. Colloids may be needed in severe cases. Six percent hetastarch in 0.9% sodium chloride has been recommended. However, hetastarch may be contraindicated if bleeding disorders are present because it prolongs prothrombin, partial thromboplastin, and clotting times. In addition, fresh whole blood, fresh plasma, or fresh frozen plasma, may be indicated for coagulopathies.

Pit viper envenomations can result in intense pain for the patient. Analgesics may be warranted provided they do not cause respiratory depression. Aspirin and other nonsteroidal anti-inflammatory drugs with anticoagulant effects should be avoided. In human medicine, patients have reported substantial analgesia from antivenin alone.

**Antivenin.** Once stabilized, the degree of envenomation should be evaluated by analyzing laboratory data and observing the severity of systemic and local signs. Dogs that have moderate to severe degrees of envenomation should receive antivenin as long as there is no history of anaphylaxis. The same antivenin (Antivenin [Crotalidae] Polyvalent [equine origin], Fort Dodge or Wyeth) is used to treat envenomation by all of the pit vipers. Copperhead envenomations have proven to be much less toxic than the other pit vipers and can usually be treated conservatively without the use of antivenin.

Although the use of antihistamines is controversial, many practitioners administer H blockers such as diphenhydramine to calm the animal and pretreat against allergic responses to the venom. The antivenin package insert gives instructions on performing the skin test for horse serum sensitivity prior to administration. This test is simple to perform and should be utilized on all patients. However, it is not completely reliable and many false-positive and false-negative test results occur. Initially, at least one vial of antivenin should be delivered intravenously. By comparison, as many as 20 vials of antivenin may be used in humans that have been bitten by rattlesnakes. Due to the lack of venom dilution, smaller patients and patients that are bitten on digits may require 50% more antivenin than bites in larger animals or bites excluding digits.

The antivenin should be added to the intravenous fluids and delivered slowly over one or more hours while monitoring for signs of anaphylaxis. Hyperemia of the inner pinna is a good indicator of a systemic reaction. In mild cases of anaphylaxis, slowing the rate of administration may be all that is necessary to relieve the symptoms. Antihistamines are of little value unless given before the antivenin. Epinephrine is the drug of choice for anaphylaxis and should be readily available during treatment. If swelling increases, coagulopathies continue, or any other problem worsens, an additional vial of antivenin is probably warranted. Platelet numbers may be a good indicator of the progress towards recovery for the patient during treatment.

The amount of time from envenomation to the delivery of the antivenin is crucial to the overall prognosis in these cases. It was found in a study of eastern diamondback rattlesnake (Crotalus adamanteus) envenomation in dogs that if antivenin was given 30 minutes after subcutaneous venom injection, eight out of eight dogs survived. If the antivenin was administered four hours after envenomation, five out of eight dogs survived; if given at eight hours, only one dog survived.

**Corticosteroids.** The use of corticosteroids is the most controversial issue among clinicians who treat pit viper envenomation. Support both for and against steroid use can be found in the literature. The majority of publications do not recommend the use of corticosteroids except in patients that are in shock or have had hypersensitivity reactions to the venom. Corticosteroids are not used to treat envenomation in human patients. Historically, corticosteroids have been the cornerstone of treatment for venomous snakebites.
The ability to block the action of phospholipase A, the major active component of most snake venom, would seem to be an advantage of steroid use. Disadvantages of corticosteroids include the impairment of wound healing, the masking of clinical signs and infections, the alteration of important laboratory data, and the possibility of interfering with the binding of antivenin to venom.

**Antibiotics.** It has been shown that a wide variety of both aerobic and anaerobic bacteria can be found as part of the natural flora of a snake’s mouth. Bacteria of major concern are *Clostridium* species and *Pseudomonas*. The choice of antibiotic should be based on culture and sensitivity testing of the bite wound. Broad spectrum antibiotic therapy is recommended pending test results.

**Conclusion**

The diagnosis and treatment of pit viper envenomation in dogs can be very challenging. The wide variety of clinical signs and degrees of toxicity can make each case vastly different in presentation and response to treatment. It is important for the clinician to be familiar with the pathophysiology of envenomation in order to understand the multisystemic effects that may be presented. The clinician should become knowledgeable about the poisonous snakes in the area and the idiosyncrasies of their venom components in order to make educated decisions regarding therapy for their victims.

**References**


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**Dr. Adams, continued from page 6.**

lab in large dumpsters, on that particular year, I managed to have Wolfgang wheel in a dumpster with me in it dressed up in a mask and such, and when he wheeled in the cart to freshman lab, I jumped out and scared all the freshman."

Dr. Adams feels happy to have had a chance to provide laboratory instruction with not just embalmed cadavers but has been able to provide more fresh or non-embalmed cadavers.

Dr. Adams has been an almost institution for freshman veterinary students at the Iowa State University College of Veterinary Medicine and he will be sorely missed. We wish him good luck with future endeavors and we look forward to using the interactive CD-ROM instructional programs. Best wishes with your move and enjoy the fishing wherever it may take you! ☝

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