Snake Envenomation in the Dog

Adam K. Wagner
Mississippi State University College of Veterinary Medicine
Class of 2017

Clinicopathologic Conference
Presented April 7, 2017

CPC Advisor:
Marc Seitz, DVM, DABVP (Canine and Feline Practice)
Assistant Clinical Professor, Emergency Medicine

Introduction

Venomous snakes are found throughout nearly the entire United States (U.S.) with an estimated 150,000 annually reported pit viper bites in companion animals. (1) The two families of venomous snakes in the US are the Crotalidae (pit vipers) and Elapidae (coral snakes). Nearly 99% of all snake envenomations in the U.S. are caused by pit vipers. The pit vipers are further divided into three genera *Crotalus* and *Sistrus* (rattlesnakes) and *Agkistrodon* (copperheads and water moccasins). Rattlesnake envenomations have the highest mortality rates. (2) The overall canine mortality rate for pit viper envenomations is thought to be as high as 30%. (4)

Pit vipers are named because of the pit (a heat receptor organ) located between the eye and nostril. They have triangular shaped heads as well as vertically elliptical pupils. Pit vipers also possess 2 long maxillary teeth that are able to fold back into the mouth when it is closed and rotate perpendicular to the maxilla when the snake goes to strike. The penetration of these fangs into the victim allows for envenomation. It has been reported that pit vipers are able to strike at a distance equal to half their own length and do so at speeds of up to 8 feet per second. (1) Pit vipers have the ability to deliver only part of their venom at a time and up to 25% of all bites are ‘dry’ and carry no venom. (4)

Coral snakes account for a very small percentage (<1%) of snake envenomations in the US. (2) They differ from pit vipers by lacking a pit on their face, having round pupils, and fixed fangs. They are also unable to deliver venom through a quick strike and must instead chew upon their victim for envenomation to occur. (4)

History and Clinical Presentation

The history that accompanies cases of snake envenomation can be quite varied. Some involve the owner seeing the strike occur, while others may just hear the dog react to the bite. Other times the dog is out alone in the yard and the owner may notice swelling or lameness after the bite. Still other cases involve owners who do not notice anything wrong until the more severe clinical signs appear from the venom.

Dogs can present with many clinical signs depending on the type of snake and the severity of the envenomation. Pit viper venom has been shown to contain more than 50 different enzymes that affect a myriad of body systems. Examples include the coagulation, muscular, cardiovascular, respiratory, and nervous system. (1) The effects of the bite and envenomation can be either local or systematic. Envenomation can cause severe edema and swelling at the bite location as well as pain, ecchymosis, and eventually local tissue necrosis. If the venom spreads throughout the body, systemic signs can be seen. These can include vomiting, respiratory distress, muscle fasciculation, diarrhea, hemorrhage, cardiac arrhythmias, obtundation, and hypotension. (4, 9) Systemic clinical signs result from a systematic inflammatory response to the venom and subsequent organ dysfunction (i.e. multi-organ dysfunction syndrome). Rarely, even severe pit viper envenomations can show slight to no local tissue involvement but eventually cause severe systemic signs. (4)

Most patients begin showing clinical signs within 30 minutes of the envenomation. (1) However, clinical signs may be delayed for hours after the bite. Therefore, all suspected envenomations should be monitored for at least 8 hours before discharge (and ideally for 24 hours) to monitor for any developing clinical signs.

Pathophysiology

Pit vipers inject venom into prey via 2 retractable fangs on the maxilla which enters the vascular and lymphatic system and thus spreads throughout the body. (1) The purpose of venom is twofold. First, it helps immobilize prey. Second, it shortens the digestion process from as long as 14 days to as little as 2-5 days. (4) Shortened digestion times are possible because pit viper venom contains over 50 enzymes capable of breaking down many of the prey's body systems. The destructive properties of these enzymes is what cause the local and systematic clinical signs seen in envenomated dogs. (1)

Of the many enzymes present in Pit viper venom, a few will be highlighted to help illustrate the pathophysiology of envenomation. Metalloproteinases hemorrhagin 1 and 2 have been shown to disrupt platelet function as well as prolong both prothrombin time (PT) and partial thromboplastin time (PTT). (8) Phospholoipase A2 is responsible for red blood cell abnormalities (echinocytes, spherocytes), platelet aggregation, and thrombocytopenia. Proteases cause soft tissue damage and results in necrosis. (1) Hyaluronidase decreases the strength in connective tissue which results in breakdown of bonds between the tissues and allows the venom to spread more easily throughout the body. (2) Metalloproteinases cause necrosis at the site of envenomation and also cause systemic inflammation which leads to further tissue necrosis. (2) These are just a few of the many enzymes found in pit viper venom.

Differential Diagnosis

Differential diagnoses for snake envenomation in the dog can include envenomation by insects or arachnids, trauma (especially bites from other animals), a draining abscesses, cellulitis, or a coagulopathy. (2)

Diagnostic Approach/ Considerations

Many different diagnostics can be used to help diagnose snake envenomation. A good history and physical exam are the first line of diagnostics. Physical exam findings that support envenomation include local swelling, and pain with centralized bite marks. While the physical may not yield puncture wounds from the snake, it also helps to evaluate the overall status of the patient. (2) Of particular importance are auscultation of the heart and lungs, pulse quality, mucous membrane color, capillary refill time, and identification of any petichiation. A good baseline physical exam can help to determine what therapy is necessary to help support the patient. Serial exams can also help monitor clinical progression and determine the patient's response to treatment.

The severity of the clinical signs at the time of presentation determines the order and use of diagnostics. Stabilizing the patient is the first priority and will be further discussed later. Once this is accomplished, further diagnostics may be performed. A CBC, chemistry, and urinalysis should be obtained. The CBC will likely show anemia from either hemorrhage or leakage out of the vasculature into surrounding tissues. (4) A leukocytosis may be seen and is caused by either stress or inflammation secondary to inflammatory mediators present in the venom. Thrombocytopenia caused by the venom is commonly seen. (8) A chemistry profile often shows an elevated creatinine kinase from tissue damage, azotemia from dehydration, poor renal perfusion, or acute kidney injury, and hypoalbumenia caused by vascular leakage. However, other non-specific changes are also possible depending on how systemic the patient is affected. (8) Urinalysis can often show myoglobinuria, hemoglobinuria, or proteinuria. (8) A blood smear should also be performed as morphologic changes to red blood cells ae common. (8) For example, it has reliably been demonstrated that the widespread presence of echinocytes is

indicative of rattlesnake envenomation; however, the absence of echinocytes does not rule out the process. (6)

One of the most affected body systems with pit viper envenomation is coagulation. Enzymes present in the venom can cause prolongation of both prothrombin time (PT) and partial thromboplastin time (PTT). (8) Pit viper venom can also cause an increase in d-dimer concentration and other fibrin degradation products (FDPs) as certain enzymes are fibrinolytic. In certain cases, PT and PTT will be prolonged with no to few detectable FDPs present. This has been attributed to anticoagulant enzyme activity in the venom rather than consumption coagulopathy. (8) Venom can cause a procoagulant state in the body which can eventually lead to disseminated intravascular coagulation (DIC). (8) Venom induced consumptive coagulopathy (VICC) has been described in certain pit viper envenomation cases. VICC is related to DIC, but does differ in the general lack of systemic microthrombi and the site of procoagulant activation in the coagulation pathway. Cases of VICC tend to be less severe than DIC because of the lack of microthrombi. (8)

Treatment and Management

Treatment of snake envenomation relies heavily on supportive therapy, antivenom administration, correcting any coagulation deficits or severe anemia, analgesia, and good nursing care. There is a snake bite severity score system that allows the veterinarian to quantitatively assess of the patient at presentation and also monitor progression and response to treatment. (2)

Fluid therapy is the cornerstone of supportive therapy. Stable patients benefit from intravenous fluids to support tissue perfusion and to help promote diuresis. Pit viper envenomation can often cause severe hypotension from hemorrhage or fluid shifts from vascular

leakage into tissues. Hypovolemic shock should be corrected rapidly with the intravenous administration of balanced isotonic crystalloid boluses. Typically, a one-quarter shock dose (shock dose-90 ml/kg) is given and the patient reassessed afterwards. Further fluid boluses can be administered as needed. (1) Colloids should not be used as they may leak into tissues and work to cause further hypovolemia due to their osmotic effects. (4)

Antivenom is the ideal treatment for pit viper envenomation. Neutralization of the venom is able to halt and even reverse coagulation abnormalities, mental impairment, arrhythmias, and prevent further tissue necrosis. (2) Antivenom should be administered to the patient as soon as possible with the ideal administration occurring within four hours of the bite, but can still be effective as long as venom is still circulating in the patient. (1) The antivenom should be diluted with one vial to 100-250 ml of a crystalloid. (4) The ideal rate of administration has not been found, but it has been reported that as long as the patient tolerates the antivenom, it can be given as quickly as 1 hour. Anaphylaxis is a rare side effect of antivenom administration and can cause clinical signs such as vomiting, hypotension, and shock. If signs of anaphylaxis are observed, the antivenom should be stopped and the patient treated with epinephrine and diphenhydramine. (1)

There are only two approved antivenom products in the US. (1). Antivenin Crotalidae Polyvalent (ACP) is made by taking complete immunoglobulin and albumin from horses that have been immunized to the western diamondback rattlesnake, eastern diamondback rattlesnake, South American rattlesnake, and the Fer-de-lance. (2) The dosage of ACP in the dog varies by the size of the dog and the severity of the envenomation. The range is from 1-10 vials and is based upon clinical signs and how quickly the animal improves. The large size of the molecule and the presence of albumin cause ACP to carry a higher risk of allergic reaction during administration. (1)

Crotaline Polyvalent Immune Fab (Crofab) is made by taking immunoglobulin from sheep that have been immunized to the western diamondback rattlesnake, eastern diamondback rattlesnake, Mojave rattlesnake, and cotton-mouth. (2) Part of this immunoglobulin is cleaved off to decrease the size of the molecule. There is also no albumin present in the Crofab antivenom. The smaller size and lack of albumin decrease the antigenicity of the antivenom. Crofab is also reported to be 5.2 times as potent as ACP which allows for fewer vials to be used. However, the smaller size allows the antivenom to be excreted quicker repeat dosing may be necessary. (1)

Antivenom administration should result in slowing and eventually halting of the coagulation impairment. (7) Fresh frozen plasma is sometimes used to provide increased coagulation factors. However, it has been noted that a procoagulant effect resulting in increased fibrinolysis can occur with the interaction between FFP and venom still active in the patient. (1) If bleeding has resulted in a clinical anemia, it may also be necessary to administer whole blood or packed red blood cells. It should also be noted that any transfusion has the potential to result in adverse effects such as a transfusion reaction.

The need for antibiotics with snake envenomation cases is controversial. It has been standard practice to administer antibiotics to all snake envenomations. (2) However, a prospective observational study involving 102 dogs that did not receive prophylactic antibiotics following rattlesnake envenomation showed that only 1 of the dogs developed an abscess at the bite site. Widespread local tissue necrosis and abscess formation at the site would require antibiotics, whereas the majority of cases will not require prophylactic antibiotics. (5) The use of antibiotics is at the discretion of the treating veterinarian based upon the extent of the tissue damage and overall condition of the patient.

Snake envenomation can be extremely painful and it is necessary to provide analgesia. Full mu opioids such as methadone, hydromorphone, and morphine all provide appropriate analgesia. These may be administered intermittently or as a constant rate infusion (CRI). A fentanyl CRI is very efficacious. A lidocaine CRI can also be used in conjunction with an opioid. (1) Nonsteroidal anti-inflammatory drugs should not be used during treatment as they can further inhibit platelet function and lead to increased coagulation deficits. (1)

The use of glucocorticoids in cases of snake envenomation is a much debated treatment. Most studies seem to show that there is no effect or in some instances a negative effect on the patient. (1) A study of a pit-less viper whose venom shares many characteristics to pit vipers, the European adder, involving a single prednisolone injection given to dogs following envenomation showed no significant benefit or detriment to the outcome of the patient. (10) There may be some benefit reported from high doses of hydrocortisone or administration of dexamethasone, but further studies need to be done. The main theoretical benefit from glucocorticoid use seems to be in treating the effects of type I and III hypersensitivity reactions caused by antivenom. At this time, no consensus exists as to whether or not steroids should be used. (1)

Expected Outcome and Prognosis

The outcome and prognosis of snake envenomation is dependent upon multiple factors. The type of snake, amount of venom injected, location of the bite, size of the victim, and the timeliness of treatment all affect the prognosis. Rattlesnake bites tend to be more severe on average than water moccasin bites which in turn are usually more severe than copperhead bites. (9) The amount of venom that is injected depends upon the maturity of the snake, the amount of

time since the snake last ate or bit, and the snake's reason for the bite. Younger snakes typically have less restraint when injecting venom so a larger dose may be spent. (1) It can take up to 21 days to fully replenish expended venom. (2) Therefore, a snake that has recently fed may inject a smaller quantity of venom in a subsequent bite. As pit vipers can control the amount of venom injected, their intentions when they strike carry different consequences. A snake striking for defensive purposes often does so without envenomation while an offensive strike will most likely carry a measured dose of venom. However, agonal bites carry nearly the entire amount of venom. (3)

The location of the bite can cause even less severe envenomations to become quite serious. Nearly 80% of snake bites in dogs occur on the head. Such bites can cause enough swelling and edema to impede air flow, although this is uncommon. However, the large amount of vascularization in the head and neck can allow the venom to quickly spread systemically. (1) Smaller dogs often have increased concentrations of venom per kilogram. Therefore smaller dogs can have more severe signs after envenomation than larger dogs and these small dogs can require more vials of antivenom. (4) One of the most important factors in determining prognosis is the timeliness of appropriate treatment. The more time that elapses between envenomation and receiving appropriate care (fluids, antivenom) the worse the prognosis. (2)

Conclusion

Pit viper envenomation is common enough throughout the US that most practitioners will encounter such a case. There are many components of venom and this can lead to numerous clinical signs upon presentation. It is important to remember that time between being bitten and treatment is the most important factor in minimizing the effects of the venom. Antivenom administration is the gold standard for treatment and should be pursued for the best possible

outcome. Supportive care including fluid therapy and analgesia is also helps lead to a positive outcome. The prognosis for the patient depends on many factors, but with timely and aggressive treatment the outcome is usually good.

References

1- Armentano RA, Schaer M. Antitoxins and antivenoms. In: Silverstein D, Hopper K, eds. Small Animal Critical Care Medicine, 2nd ed. Elsevier 2014; 912-917

2- Peterson ME. Snake Bite: North American Pit Viper. In: Peterson ME, Talcott PA, eds. Small Animal Toxicology, 3rd ed. Elsevier, 2013; 783-797

3- Peterson ME. Snake Envenomation. In: Silverstein D, Hopper K, eds. Small Animal Critical Care Medicine, 1st ed. Elsevier, 2008; 399-405

4- Gilliam DVM, Lyndi L. and Jill A. Brunker DVM. North American Snake Envenomation in the Dog and Cat." Veterinary Clinic Small Animal 2011; 41(6): 1239-1259

5- Carr A., Schultz J. Prospective evaluation of the incidence of wound infection in rattlesnake envenomation in dogs. Journal of Veterinary Emergency and Critical Care 2015; 25(4): 546-551

6- Brown D.E., Meyer D.J., Wingfield W.E., Walton R.M. Echinocytosis associated with rattlesnake envenomation in dogs. Veterinary Pathology 1994; 31:654-657

7- Armentano R.A. and Schaer M. Overview and controversies in the medical management of pit viper envenomation in the dog. Journal of Veterinary Emergency and Critical Care 2011; 21(5): 461-470

8- Goddard A., Schoeman J.P., et al. Clinicopathologic abnormalities associated with snake envenomation in domestic animals. Veterinary Clinical Pathology 2011; 40(3):282-292

9- Senter D. and Carson T. Pit viper envenomation in dogs: Pathophysiology and treatment. Iowa State University Veterinarian 1999; 61(1): 21-26

10- Brandeker E., et al. The effect of a single dose of prednisolone in dogs envenomated by *Vipera berus*- a randomized, double-blind, placebo-controlled clinical trial. BMC Veterinary Research 2015; 11(44)