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RATTLESNAKE ENVENOMATION: PATHOGENESIS AND TREATMENT

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INTRODUCTION
There are 14 – 15 families of snakes. Four of these families contain the majority of the commonly known snakes.
1. Boidae – constrictors eg. Pythons and boas
2. Colubridae – back fanged, mostly harmless eg. Whip, grass and garter snakes
3. Elapidae – small front fanged snakes eg. Coral, cobras, kraits, mambas and sea snakes
   Two subfamilies
   (a) Viperinae – ‘True’ vipers
   (b) Crotalinae – Pit vipers eg. Rattlesnakes, copperheads & moccasins

There are approximately 115 species of snakes in the United States, 19 of which are considered venomous. The venomous snakes of North America include coral snakes of the Elapidae family and pit vipers of the Crotalidae subfamily. Coral snake bites are uncommon in veterinary medicine and will not be discussed here.

CROTALIDS (PIT VIPERS)
Pit vipers are so called because of a pit-like depression located midway between the eye and the nostril. This is a heat-sensing organ which locates the prey and guides the direction of a strike. All vipers have long front fangs that fold against the roof of the mouth. The rattlesnakes are distinguished from the other crotalids by the presence of a rattle at their tail tip.

CROTALID VENOM
Crotalus venom has two main objectives. The first is to rapidly disable the prey and this is achieved by hypovolemia and hypotension. The second objective is to initiate digestion of the prey by tissue necrosis.
All snake venoms are complex mixtures of enzymes, high molecular weight proteins and small peptides. It is important to realize that the specific action of any individual snake’s venom cannot be predicted due to large inherent variability. The main actions of crotalid venom can be divided into 5 categories. The venom of individual crotalid species will have some or all of these actions.
1. Cytotoxicity
2. Endothelial damage
3. Coagulation abnormalities
4. Thrombocytopenia
5. Myonecrosis
6. Neuropathy

CLINICAL SIGNS
The clinical signs observed in a patient following a pit viper bite will depend on the type of snake involved, the time since the incident, the severity of the envenomation and the anatomical site of the bite. A pit viper bite will leave fang wounds. These can usually be found if the coat is clipped and thoroughly explored. Often these puncture wounds are bleeding and the bitten area is extremely painful. The speed of progression of clinical signs is related to the severity of the envenomation. Severe envenomations will have local and systemic signs within 30-60 minutes of the bite, less severe bites may take 6-8 hours for the development of overt clinical signs. Systemic signs can have a slow and insidious onset many hours after the initial local signs have been noticed. For this reason any animal suspected to have been bitten by a snake should remain under close observation for up to 8 hours following the incident.

The local reaction involves swelling and edema of the tissue around the bite site. This will often progress to ecchymosis and discoloration of the skin. The swelling can progress for 24 – 36 hours if untreated and when bitten around the face and neck the swelling can lead to respiratory distress. In time, areas of discolored skin can progress to become black and necrotic.
Cardiovascular compromise is characterized by vasodilation, hypovolemia, tachycardia, and hemoconcentration. In severe cases the degree of shock is life threatening and will be fatal without therapy.
If the snake venom contains a neurotoxin, a progressive flaccid paralysis may be observed. The speed of progression is proportional to the severity of the bite. Victims of severe envenomations can die from respiratory muscle paralysis if not supported with mechanical ventilation. Often venoms with neurotoxic effects will have minimal local effects.

DIAGNOSIS
Diagnosis of snake bite in animals is largely presumptive. The history may be of some assistance. The majority of snake bites occur in the spring and summer and bites are more common in rural areas. The owners may have witnessed the bite or observed a snake in the vicinity of the animal.
Any focal region of swelling, pain and skin discoloration should warrant a close examination for evidence of fang wounds and consideration of the patient history. A concurrent thrombocytopenia and/or hypofibrinogenemia is highly suggestive of a pit viper envenomation. Viper venom has been found to cause erythrocyte membrane abnormalities and lead to the development of echinocytes. This is not a consistent finding in envenomated animals. Response to antivenom therapy is another diagnostic tool.

TREATMENT
First aid is an important topic in human medicine but it is not as relevant in veterinary medicine. The only intervention that has been found to improve the outcome in snake bite victims is early medical intervention. For this reason first aid that is likely to delay the transport of an animal to a veterinary facility is contraindicated.
Animals that have received a significant pit viper bite will be in shock. Fluid resuscitation is essential. Blood samples should be collected as is feasible to establish base line values and they may also provide some indication of the severity of the bite.
Antivenom administration is the only therapeutic intervention which has been proven to be of benefit in the treatment of venomous snake bite. Although there are many cases of animals which have successfully survived a rattlesnake bite with supportive therapy alone, severity of an envenomation can be difficult to determine in the first few hours. As antivenom therapy is always more effective the earlier it is administered it should be recommended in all envenomations. If antivenom therapy cannot be given for
financial reasons, aggressive supportive care and adequate analgesia should be provided as many cats and dogs can be nursed through a rattlesnake envenomation.

POLYVALENT CROTALIDAE ANTIVENOM

The conventional polyvalent crotalidae antivenom, manufactured by Wyeth-Ayerst Laboratories is made from hyperimmune equine serum with venom from the western diamondback rattlesnake, eastern diamondback rattlesnake, the tropical rattlesnake and the Fer-de-Lance. Most if not all pit viper venom shares some common antigens so the antivenom is effective against other venoms from this family. This antivenom is a solution of IgG and other serum proteins, mainly albumin.

Polyvalent crotalidae antivenom should be reconstituted according to the manufacturer’s instructions. The vial cannot be shaken when reconstituting as this will produce a stable foam preventing aspiration into a syringe. Following reconstitution of the antivenom with the diluent the solution should be given some time to allow the protein to dissolve. Up to 90 minutes may be required but in urgent situations a delay of 10 – 15 minutes will significantly increase the efficacy of the antivenom. The reconstituted antivenom should then be diluted in an isotonic crystallloid solution such as 0.9% sodium chloride. A minimum dilution of 100-200 ml is ideal. This volume should be reduced accordingly in very small patients. The diluted solution should initially be infused slowly intravenously while the patient is monitored for adverse reactions. If the initial 15-30 minutes of infusion is uneventful then the rate of infusion can be gradually increased. Intradermal testing has been shown to be an unreliable indicator of an immune reaction and is no longer recommended. The amount of antivenom to give will depend on clinical judgement and the financial constraints of the owner. Human victims of a pit viper bite are given a minimum of 5 vials of polyvalent crotalidae antivenom. Moderate envenomations are given ~10 vials and severe envenomations are given at least 15 vials. Antivenom therapy will be repeated if the patient is not showing an adequate response to therapy within several hours. In veterinary patients one vial is the likely starting point. In animals with severe envenomation, evidenced by significant systemic signs a short time after the bite, an initial dose of 2 vials should be considered. Smaller animals are likely to have suffered a higher venom dose on a per kilogram basis. As a result a larger antivenom dose may be indicated in these patients. Antivenom therapy can be of benefit up to 60 hours following a bite.

CROFAB ANTIVENOM

Crotalidae polyvalent immune Fab-ovine (CroFab®, Protherics) antivenom is a new product made from hyperimmune sheep serum to the venom of Western Diamondback, Eastern Diamondback, Mojave rattlesnakes and the Eastern Cottonmouth. This antivenom contains purified Fab antibody fragments with very little serum protein contamination making it a less antigenic product. On a per vial basis it is reported to be ~ 5 x more potent than the polyvalent crotalinae antivenom. As with the traditional product the vial should be reconstituted carefully, avoid shaking and give the product some time to become solubilized. CroFab will dissolve more rapidly than the polyvalent product, 40 minutes is ideal but waiting at least 10-15 minutes is recommended.

The CroFab product has a much shorter half life than the polyvalent crotalinae product and it is administered every 6 hours in human patients to prevent recurrence of clinical signs. It is also significantly more expensive than the traditional antivenom.

SUPPORTIVE CARE

Antihistamines are commonly used in the management of snake bite. They can provide some sedation in a distressed animal and are often chosen in an attempt to prevent anaphylaxis to the antivenom. One study found that dogs given phenergen and antivenom died sooner than those animals treated with antivenom alone. This may have been due to the hypotension produced by the antihistamine. Currently antihistamines are only recommended in human snake bite victims if there are signs of reaction to the antivenom. The antivenom is stopped and histamine 1 and histamine 2 blockers are given (+/- epinephrine) and the patients are observed closely. If the patient improves the antivenom infusion is continued at a slow rate.

Corticosteroids are the most controversial topic in snake bite therapy. In the literature there is no evidence demonstrating that corticosteroids provide benefit to humans or animals with crotalid bites. Several of these studies have found that patients treated with corticosteroids and antivenom have a higher morbidity and mortality than those treated with antivenom alone.

Pain is a major clinical sign following envenomation. In human medicine, a reduction in the degree of pain association with a snake bite is seen as an indication of adequate antivenom administration. In veterinary medicine pain can make patients very difficult to handle and treat. Analgesia is often an important therapeutic consideration. Opioids such as hydromorphone, butorphanol or buprenorphine are recommended as they can provide analgesia with minimal cardiovascular effects.

Broad spectrum antibiotics are advised as snake mouths are known to contain numerous pathogenic bacterial, predominantly gram negative bacteria. As a snake bite lesion progresses and there is tissue death present, secondary infection of the area is a risk.

In the past crotalid bites have sometimes been treated with surgical debridement. This has been found to substantially increase morbidity and mortality compared to antivenom therapy alone and is not advised. Fasciotomy to relieve pressure in swollen tissue (compartment syndrome) has also been found to contribute to morbidity and can often result in greater tissue trauma than the necrosis and damage due to the venom alone. Progressive tissue swelling is most effectively treated with further antivenom administration. Tissue edema and swelling will resolve in 7-10 days if sufficient supportive care is provided.

MONITORING

Monitoring of envenomated animals includes both clinical evaluation and laboratory tests. Clinically the cardiovascular status of the patient needs to be closely monitored as hypovolemia and hypotension are known causes of death. Progressive swelling at the bite site can be monitored by measuring the circumference of the limb. If it continues to progress for 1-2 hours following antivenom therapy, another dose of antivenom should be considered. Swelling around the upper airway compromising the animals respiratory function may require the placement of a temporary

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tracheostomy tube. Frequent measurement of packed cell volume, total protein, clotting time, platelet counts and fibrinogen levels are recommended. An ongoing fall in platelet count and/or fibrinogen levels may be an indication for further antivenom therapy.

REFERENCES