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ZOOTOXINS AFFECTING ANIMALS – A REVIEW

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ABSTRACT

The animal kingdom is populated by a vast variety of creatures. Every phylum within the animal kingdom contains species that produce poisons or venoms. Poisons are compounds produced in non-specialized tissues as secondary products of metabolism that accumulate in the host animal or that accumulate in predators following ingestion of prey. In contrast, venoms are produced in specialized tissues or glands, and venomous animals have developed a variety of venom apparatuses to deliver their venom to target animals—a process termed envenomation. Most venoms and poisons are not composed of a single chemical substance but, rather, are mixtures of a variety of chemical compounds like peptides, amines, serotonin, quinones, polypeptides and enzymes that often act synergistically to produce their toxic effects. These compounds are collectively termed toxins and toxins produced by members of the animal kingdom are collectively termed zootoxins. Bites and stings from arthropods and snakes certainly can occur in any species, and the potential for oral exposure to animals such as poisonous toads, snakes, or insects will vary with the region and environment.

Keywords: Zootoxins, Animals

INTRODUCTION

Zootoxins can be divided into several categories: (1) oral poisons—those that are poisonous when eaten; (2) parenteral poisons, or venoms—those that are produced by a specialized poison gland and administered by means of a venom apparatus; and (3) crinotoxins—those that are produced by a specialized poison gland but are merely released into the environment, usually by means of a pore. Oral zootoxins are generally thought to be small molecules; most venoms are believed to be large molecules, usually a protein or a substance in close association with one. Venoms, which are produced by specialized poison glands, are injected by means of a mechanical device that is able to penetrate the flesh of the victim. Compared to other means of injury or illness in animals,

envenomation or poisoning from zootoxins is relatively rare in domestic animals, due largely to the protection provided by animal owners (Dorce *et al*., 2009; Gwaltney-Brant *et al*., 2017). Wildlife, on the other hand, probably faces exposure to potential zootoxins on a frequent basis.

Epidemiology of poisonous animals

Animal bites and stings contribute significantly to mortality in certain parts of the world. India accounts for the highest number of snakebites and related mortality globally. The annualized mortality rate per 100,000 population due to snakebite, scorpion sting and other animals. Deaths due to bite/sting of a venomous animal accounted for 10.7% of all unintentional injuries, with an adjusted mortality of 6.2 per 100,000 population (Dandona *et al.,* 2018). Following the World Health Assembly of May, 2017 snakebite was finally included in the World Health Organization (WHO) list of Neglected Tropical Diseases and in May 2019 the WHO launched the official snakebite envenoming road map with the ambition to reduce the number of deaths and disabilities by 50% before 2030 (WHO, 2019).

Effects of poisonous secretions

The main effect is neurotoxic because it acts on the calcium channels of the neurons, causing incomplete activation of the same, presenting repetitive discharges in the axons (Garcia *et al.,* 2019). Exposure to zootoxins occurs through five routes such as:

a. Digestive tract: dogs and cats play and consume rodenticide dead rodents, toads, wasps, scorpions, etc.

b. Pulmonary route: If the toxic substances are in gaseous, solid or liquid state, exposure occurs by inhalation, passes to the lungs and to the blood circulation.

c. Skin: When the skin is inflamed it is vulnerable to the action of toxic agents.

d. Transcutaneous route: Exposure in this way is through bites, bites: insects or animals, when injecting their poison directly.

e. Parenteral route: allergic reactions.

Spiders

At least 30,000 species of spiders are distributed throughout the world (Goddard, 2003). Although there is disagreement in the literature, it appears that fewer than 100 spider species can inflict a bite of medical significance (Lucas and Meier, 1995b). Of various poisonous spiders, black widow spider, brown recluse spider, red widow spider, red-legged spider, desert violin spider and cobweb spider have been implicated in bites. Venom is stored in two glands located

in the cephalothorax and empties through fangs (chelicerae) located at the rostral end of the prosoma. The venom gland contains just less than 0.2mg of venom. The venom of widow spiders is extremely potent; the LD50 for whole venom of European black widow in guinea pigs is 0.0075 mg/kg and for mice is 0.9 mg/kg (White *et al*., 1995). The syndrome caused by widow venom is called latrodectism. Following a widow spider bite, venom is taken up by lymphatics and then enters the bloodstream. Clinically, there may be short-lived, localized pain at the bite site followed in approximately 30-120 min by myalgia and muscle cramps near the site of envenomation. Pain begins to spread to the large muscles groups of the legs, thorax, back, and abdomen, peaking in approximately 2-3 h. Mild to moderate hypertension and tachycardia are common. In most cases, signs resolve in 48-72 h, but signs such as weakness, fatigue, and insomnia may persist for weeks to months.

The venom of spiders is a complex mixture of neuroactive proteins and other chemicals. Among various proteins, α-lactrotoxin, a liable neurotoxin is the most potent toxin which acts at the neuromuscular junctions and causes the release of Ach from pre-synaptic nerve fiber. The release and subsequent depletion of Ach results in severe painful cramping of all large muscle groups (Lucas and Meier, 1995b). The neurotoxins bind to glycoproteins or gangliosides on neuromuscular synaptic membranes and allow opening of cationic channels. Calcium-channel binding increases the membrane's permeability to calcium and enhances depolarization.

Cats are very sensitive to the effects of widow venom (Peterson and McNalley, 2006a). Signs include regional numbness, cramping of the abdominal, lumbar, and thoracic muscles, possible respiratory distress, seizures, and extreme pain. Abdominal rigidity in the absence of pain or tenderness, has been dubbed a hallmark sign of widow spider envenomation.

Treatment is primarily symptomatic and supportive. Calcium gluconate, which was once used for treatment of widow envenomation, is no longer recommended because it was found to be less effective at controlling pain than opioids and muscle relaxants (Clarke *et al*., 1992; Peterson and McNalley, 2006a). Supportive care includes diazepam and methocarbamol for muscle relaxation and opioids for analgesia. An equine-origin antivenin has been used in humans. Drugs that disrupt coagulation should be avoided in cases of systemic toxicity.

Scorpions

Scorpions are arachnids. They have large claws or pinchers with which to grasp

prey but, more concerning, is the telson. The telson is an appendage attached at the caudal abdomen which contains two venom glands and a stinger. Hence, scorpions do not "bite," they "sting." They may also hide in blankets, shoes, and clothing, which is a common way for humans to be exposed to them (Keegan, 1980). Black bark scorpion (*Centruroides exilicauda*) found in Mexico and *Leiurus quinguestriatus* found in Asia and Africa cause severe poisoning in humans and animals.

Scorpion venom components vary greatly between genera and may even differ based on geographic location within species (Mullen and Stockwell, 2002). The venom consists of a mixture of low-molecular-weight polypeptides. At least two potent neurotoxins have been identified: α-scorpion toxin found in Androctonus, Leiurus, and Buthus spp. and β-scorpion toxin found in Centruroides spp. These venoms block voltage-sensitive sodium and potassium channels in nerves (Mullen and Stockwell, 2002).

Scorpion stings cause instant, sharp pain at the site of envenomation. Localized oedema and pruritus are common. Regional lymph nodes may enlarge, and there may be an allergic reactions, sloughing of the skin at the site of envenomation can also occur. Signs usually resolve within 24 h. Common CNS signs include nystagmus, paresthesia, referred pain and asymmetric jerking of the limbs. Other sings include excessive salivation, tachycardia, fever, hypertension, and increased respiratory secretions.

Treatment is primarily symptomatic and supportive. In human beings, antivenom is gaining popularity and success. However, their use in veterinary patients is considered controversial (Dalefield and Oehme, 2006).

Ticks

Ticks are well known as being vectors for many human and animal diseases, with the first reports of tick paralysis originating in Australia in 1890 and British Columbia in 1912 (Sonenshine *et al*., 2002). Worldwide, 43 species of ticks from nine different genera have been associated with tick paralysis: Amblyomma, Argas, Dermacentor, Haemaphysalis, Hyalomma, Ixodes, Ornithodoros, Otobius and Rhipicephalus (Dipeolu, 1976; Fowler, 1993). It is during the feeding on host blood that a female tick injects the toxic saliva and produces the tick paralysis.

The toxin interferes with the synthesis and/or release of acetylcholine at the neuromuscular junctions, resulting in lower motor neuron paresis and paralysis very similar to that produced by botulinum toxin (Fowler, 1993). Dermacentor toxin is

reported to block axonal sodium channels in motor neurons. The nerve conduction blockade leads to hypotonia and hyperflexia ultimately resulting in paresis or paralysis.

Early signs include lethargy, loss of appetite, anxiety, apprehension, retching, regurgitation, groaning when lifted, weakness in limbs and ataxia. Paresis begins in the pelvic limbs and ascends. The signs may become generalized in 2-3 days with quadriplegia and paralysis of different body systems. Eventually, paralysis of the respiratory muscles leads to respiratory failure and death.

Ticks may be removed either manually or by using appropriate ectoparasiticide. Removal of ticks normally results in marked improvement in animal's condition within 1-2 days (Fowler, 1993). Hyperimmune serum if available, may be used in dogs. A short-term immunity develops following recovery from tick paralysis.

Hymenoptera : Bee, Wasps and Hornets

More than 20,000 species of bees are distributed throughout the world. Native honeybees in tropical Southeast Asia were the source of the domestic honeybee *Apis mellifera*. There are numerous variations in the venom apparatus of members of Hymenoptera (Fowler, 1993). The stinger is a modification of the ovipositor apparatus and is found only in female bees and wasps. The stinger of the honeybee is covered with retrograde barbs that cause the stinger to remain impaled in thick-skinned victims. When this occurs and the bee attempts to withdraw, the entire stinger apparatus is pulled from the bee, resulting in death of the honeybee (Gwaltney-Brant *et al*., 2017).

Honeybee venoms are complex mixtures of proteins, peptides and small organic molecules. Phospholipase A2 is one of the most lethal peptides in honeybee venom (Schmidt, 1995). Mellitin is a membrane disruptive compound that increases the susceptibility of cell membranes to the damage caused by phospholipases within the venom. Apamin is a neurotoxin that blocks calcium-activated potassium channels and has been associated with transient peripheral nerve effects in humans after bee stings (Saravanan *et al*., 2004). Like honeybees, vespid wasps (including yellow jackets and hornets) produce venoms containing peptides, enzymes, and amines designed to trigger pain. Some vespid venom contains neurotoxins or alarm pheromones that alert the swarm to an intruder.

A single bee sting will produce pain, swelling, erythema, edema and local induration which can be followed by pruritis at the injection site. In systemic toxicity,

redness or swelling at sites on body distant from the site of sting such as lips/muzzle, eyelids, tongue and vulva. Sometimes the reaction can be severe with closing of airway and perhaps shock. Immune-mediated haemolytic anaemia secondary to bee envenomation developed in two dogs (Noble and Armstrong, 1999). Acute lung injury similar to the human acute respiratory distress syndrome developed in a dog following envenomation by more than 100 bees (Walker *et al*., 2005). In rare cases, the attack is fatal. Retained stingers should be scraped away from the injection site; grasping the stinger with forceps may result in more venom being expressed into the injection site. Cold compresses may be used as first aid to relieve pain and swelling. Epinephrine may be used in cases in which anaphylaxis is suspected. Other treatments that have been recommended include corticosteroids, antihistamines, oxygen for dyspnoea and diazepam as needed for convulsions (Fowler, 1993).

Hymenoptera : Ants

There are more than 10,000 species of ants, some of which bite, some of which sting, and others that both bite and sting. Some ants that lack a sting can spray formic acid, which can cause local irritation to the victim if it gets in the eyes or wounds produced by the ant's mandibles. The red imported fire ant, *Solenopsis invicta,* is the most important species in terms of envenomation of animals. Attacks of fire ants resulting in deaths of newborn animals such as rabbits and deer have been reported (Akre and Reed, 2002). Nesting bird chicks and newly hatched quail and poultry have been killed and often eaten by fire ants (Fowler, 1993).

Fire ant venoms consist largely of alkaloids, with less than 1% proteinaceous component (Akre and Reed, 2002). The alkaloids consist of solenopsins (methyl-nalkylpiperidines) and a piperidine that cause dermal necrosis when injected in skin. These alkaloids have cytotoxic, hemolytic, fungicidal, insecticidal and bactericidal properties.

The typical reaction to fire ant sting is a wheal and flare, which resolves within an hour. Pain and inflammation begin immediately. Regional reactions may be erythematous, indurated and quite pruritic. Dogs do not appear to develop the pustules described in humans; instead, they develop erythematous pruritic papules that generally resolve within 24 h (Rakich *et al*., 1993). There are no reports of anaphylaxis in animals secondary to fire ant stings (Akre and Reed, 2002).

Local reactions may be treated with antihistamines, topical corticosteroids, water or alcohol compresses, ice, menthol and camphor. Antibiotics are indicated for

secondary infections. Adrenaline is the drug of choice for systemic reactions.

I. Amphibian : Toads

Poisonous amphibians include frogs, salamanders, and toads, but only toads have been associated with toxicosis in domestic animals. The larger toads, specifically *Bufo blombergi*, *Bufo alvarius, Bufo regularis* and *Rhinella marinus* (formerly *Bufo marinus*), are generally considered to produce sufficient poison to cause serious toxicosis (Fowler, 1993). Dogs are the species most commonly involved in toad toxicosis, with smaller dogs at higher risk (Reeves, 2004). Mouthing of toads stimulates release of toxins from the parotid gland, with absorption occurring across the mucous membranes in the mouth (Roder, 2004).

Toads produce their toxic secretions from granular glands, modified mucous glands, throughout the head, shoulders and dorsolateral areas of their skin. The more toxic toad species possess a parotid gland, which is an aggregation of granular glands located caudal and lateral to the ear (Fowler, 1993). Toad secretions contain a variety of compounds including bufogenins, bufotoxins, and bufotenines.

Bufogenins inhibit sodium-potassium ATPase activity in a manner similar to cardiac glycosides such as digitalis, ultimately causing increased intracellular calcium in myocardial cells that results in cardiac arrhythmias (Eubig, 2001). The lethal oral dose of toad venom is believed to be the entire contents of both parotid glands, or the equivalent of 0.1g of venom per dog (Revington, 2004).

Clinical effects of toad poisoning include hypersalivation, anxiety and vomiting, which can occur almost immediately following exposure; also, death may occur as rapidly as 15 min following exposure (Eubig, 2001). Other signs, including hyperemic mucous membranes, recumbency, collapse and tachypnea. A variety of cardiac arrhythmias have been reported, including bradycardia, sinus tachycardia, and sinus arrhythmias (Eubig, 2001).

On-the-spot decontamination of the oral cavity by copious water lavage is recommended in cases in which no signs beyond ptyalism and gagging have occurred. Endoscopic or surgical removal of the toad from the stomach may be required in cases in which signs have developed, but it is important to stabilize the patient prior to attempts to remove the toad.

Alternatively, multiple doses of activated charcoal with a cathartic may be used when entire toads are ingested (Eubig, 2001). Patients displaying severe signs of toxicosis should be treated symptomatically

and aggressively. Arrhythmias should be managed as they develop. Bradycardia may be treated using atropine, whereas propranolol or esmolol may be used to treat tachycardia. The prognosis for patients exposed to small toads and/or showing mild clinical signs is good. Animals developing advanced neurologic or cardiac signs have a more guarded prognosis.

Snakes

Approximately 400 of the 35,001 species of snakes in the world are venomous (Russell, 2001). Venomous snakes come from the families Colubridae, Crotalidae, Elapidae, Hydrophiidae, Laticaudidae and Iperidae. Among the domestic animals, dogs are most frequently attacked and killed by the snakes (Osweiler, 1996).

Hyaluronidase cleaves internal glycoside bonds in certain acid mucopolysaccharides resulting decreased viscosity of connective tissues allowing other fractions of venom to penetrate the tissue (Klaassen, 2008). Phospholipase A stimulates hypercontraction of myocyte membranes, resulting in myofibril rupture (Peterson, 2004). Neurotoxic components bind the presynaptic nerve membrane, inhibiting neurotransmitter release and causing paralysis (Fowler, 1993).

In studies of rattlesnake bites in dogs, most bites occurred in late spring to early fall during the late afternoon (Hackett *et al*., 2002; Witsil *et al*., 2015). Most bites involved young dogs and were located on the head. The toxicity of any given crotalid bite will depend on both victim and snake factors. "Dry" bites, those in which no venom is injected, may occur in up to 25% of snakebites (Peterson, 2004).

In most cases of snakebite, the initial signs are usually local pain and swelling, followed by petechiation, ecchymosis and discoloration of the skin in the region of the bite. Systemic clinical manifestations after being bitten include degeneration and crust in bitten area, pain, weakness, severe hypotension, dizziness, nausea, leukocytosis and thrombocytopenia (Cihan, 2004).

Crotalids (Pit viper) have elliptical pupils, triangular-shaped heads, retractable and hollow front fangs, and a single row of subcaudal scales distal to the anal plate (Peterson, 2004). Pit vipers inject their venom by rotating their retractable fangs downward and forward in a stabbing motion. Dogs are the domestic species most commonly bitten by pit vipers (Witsil *et al*., 2015).

Elapids, include cobra, mambas, kraits and coral snakes. They have short fangs and tend to hang on and "chew" venom into their victims. Head is of same

width as that of neck and pupils are circular. The venom delivery apparatus of coral snakes includes short, fixed (non hinged) front fangs that are partially covered by a membrane (Fowler, 1993). During the bite, the membrane is pushed away and the venom duct empties at the base of the fang, bathing the fang with venom that runs down grooves within the fang. Neurologic signs following envenomation may be delayed in onset for up to 12 h, and the duration of effects is prolonged (Peterson, 2004). Total clearance of venom from the body may take up to 14 days.

Neurotoxic peptides in coral snake venom cause a non-depolarizing postsynaptic neuromuscular blockade similar to the effects of curare (Peterson, 2004). Binding of neurotoxins to postsynaptic receptors appears to be irreversible.

Clinical signs vary with the species of the victim. In most cases of snakebite, the initial signs are usually local pain and swelling, followed by petechiation, ecchymosis, and discoloration of the skin in the region of the bite. Bites from snake species that possess only neurotoxic venom may show little local swelling. With Elapid bite,Catsdevelopprimarilyneurologicsigns, including progressive ascending flaccid paralysis, decreased nociperception, CNS depression, and diminished spinal reflexes (Peterson, 2004). In dogs, depression of the CNS, decreased spinal reflexes, muscle weakness, and respiratory depression may occur. Vomiting, hypersalivation, hypotension, dyspnoea, dysphagia, muscle fasciculation, tachycardia, and hemolysis have also been reported in dogs. Potential complications include dysphagia leading to aspiration pneumonia. Death is due to respiratory paralysis.

Initial first aid should be focused on keeping the animal quiet and attempting to keep the bitten area below heart level. Intravenous crystalloid therapy is recommended to manage hypotension or hypovolemia. Coagulopathy and hemolysis should be managed using blood or platelet transfusions. Corticosteroid use is controversial in snakebites, with some indicating that corticosteroids have no place in management of snakebite (Peterson, 2004), whereas others suggest that judicious use of corticosteroids may be of benefit (Fowler, 1993). Broad-spectrum antibiotics are advocated by some to aid in prevention of infection (Peterson, 2004) and horses should receive tetanus antitoxin or toxoid. The use of intravenous antivenin in crotalid snakebites can result in the reversal of potentially life-threatening problems such as coagulopathy, thrombocytopenia, and paralysis (Peterson et al., 2011). Antivenin cannot reverse tissue necrosis or secondary

effects such as renal damage.

Polyvalent snake anti-venom is preferred as it provides protection against the venom of big four species of the snakes (Suchitra *et al.,* 2010). Administration of antivenin should begin as early as possible, and patients should be closely monitored for signs of anaphylaxis during antivenin administration. Reported incidences of adverse reactions to antivenin in dogs have ranged from 0.7% to 6% (Peterson *et al*., 2011; Witsil *et al.*, 2015). The prognosis for recovery from snake envenomation is dependent on the type of snake involved, the severity of the envenomation, and the rapidity and aggressiveness of veterinary intervention.

Lizards

Venomous lizards found in North and Central America is members of the genus Heloderma. *Heloderma suspectum* and *Heloderma cinctum* are commonly referred to as Gila monsters, whereas *Heloderma horridum* is known as the Mexican beaded lizard. Venomous lizards are large and heavily bodied, with blunt, rounded tails, powerful jaws and short legs with clawed, hand-like feet. Gila monsters which can reach 55 cm in length, are smaller than Mexican beaded lizards, which can grow up to 1 m in length and weigh up to 2 kg (Cantrell, 2003; Peterson, 2004).

Heloderma spp. possesses venom glands in the lower jaw at the base of the teeth and venom is delivered through grooves in the teeth via capillary action as the lizard masticates. The venom is considered a defensive weapon rather than one for procuring food (Peterson, 2004). Heloderma venom is composed of a complex mixture of proteins and enzymes, many of which are similar to those found in snake venoms, including hyaluronidase, phospholipase A2, serotonin and a variety of enzymes (Cantrell, 2003). Gilatoxin is considered to be the major lethal factor in Heloderma venom (Fowler, 1993). Due to their inquisitive nature and tendency to harass wildlife that they encounter, dogs are the species most likely to have a significant encounter with Heloderma spp. Although rare, Heloderma bites to dogs and cats have occurred and the death of at least one dog has been reported (Fowler, 1993; Peterson, 2004).

The clinical effects of Heloderma envenomation include intense local pain, edema and hemorrhage at the site of the wound. In dogs and cats, signs may include tachypnea, vomiting, polyuria, salivation, and lacrimation. Aphonia has been reported in cats (Peterson, 2004).

Management of Heloderma bites in small animals includes initial first aid followed by assessment and monitoring. The

first course of action is often disengaging a lizard that is still attached to the victim. Suggested means of removal of the lizard include applying a flame from a match or cigarette lighter to the under jaw of the lizard, prying the jaws open with a metal bar, or killing the lizard by incising the jugular vein with a knife. The bite site should be irrigated with 2% lidocaine and the wound probed with a 25-gauge needle to detect any embedded tooth fragments (Peterson, 2006). Broad-spectrum antibiotics should be administered to prevent infection from the myriad of potentially pathogenic bacteria that have been reported to frequent the mouth of reptiles (Peterson, 2006).

CONCLUSION

Every phylum of the animal kingdom contains animals capable of producing toxic effects, either through envenomation or through poisoning. However, only a small number of these animals are sufficiently toxic. Arachnids, insects, toads, and snakes cause the most clinically significant problems for domestic and wild animals. Although in some cases specific antidotes exist for exposures to venomous animals, availability and cost of these antidotes often make their use in veterinary medicine unfeasible. Therefore, most cases of zootoxicosis in animals are often managed with symptomatic and supportive care.

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