A BRIEF REVIEW OF SNAKE VENOM

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Abstract

Snakes are members of the class Reptilia or known as the reptiles. They constitute part of the order Squamata, which also comprises the closely related lizards and amphisbaenians. Snakes, of which there are roughly 2700 species, compose the sub-order Serpentes. Since some non-venomous snakes might resemble venomous ones, there is no universal criterion for determining which ones are venomous. Nevertheless, the pattern, shape, colouration, size, behaviour, and sound of some of the most notable venomous snakes can help to identify them. This review aims to assist in better understanding about the snake species with venoms. Snake venoms are classified into three groups: those that influence the blood, tissues, and nervous system. However, there are many other different toxins within each category and some toxins may have more than one harm. As an example, damage to the vascular endothelium, erythrocytes, leukocytes, platelets, peripheral nerves, and skeletal muscle, as well as the release of inflammatory mediators, can be caused by venom enzymes, such as phospholipase A2. Antivenom is significant as it stops or reverses envenomation in patients, thus curing snake envenomation. It is an immunotherapy that binds to venom toxins, inactivating them, and accelerating their elimination by forming immunocomplexes. This is particularly significant for hospital pharmacists and physicians to administer the proper antivenom for envenomated patients.

Keyword: Antivenin, envenomation, hemotoxin, neurotoxin, snakebite, venomous snake

Introduction

Venomous snakes are snakes that can produce venom, which they employ to attack prey, defend themselves, and aid in the digesting of their prey. Elapids (kraits, sea snakes, cobras, coral snakes) and vipers are venomous snakes native to Malaysia (Tan, 2015). Venomous snakes belonging to Elapidae are identified by their fixed fangs at the front of the mouth. Viperidae, in contrast, are identified by their entirely hollow, non-grooved fangs and mobile maxillary bones. In elapids, the venom of the cobra and king cobra causes pain and tissue necrosis, whereas the venom of sea snakes may result in rhabdomyolysis and serious renal damage (Mara, 1996). Venom composition varies greatly between species, resulting in differences in the diagnosis of neurotoxic venom by different species and the efficiency of antivenins against different venoms.

According to World Health Organization (Anonymous, 2021), approximately 5.4 million snake bites occur annually, resulting in 1.8 to 2.7 million occurrences of envenomation. More than 81,000 people die yearly, with amputations and other lifelong impairments accounting for around three times that number. Snakebite envenomation remains an unsolved health issue affecting numerous impoverished populations in tropical and

subtropical regions. Due to the richness of venomous herpetofauna and the region's substantial agricultural activities, Southeast Asia is a specific hotspot for snakebites (Das, 2018). Snakebite envenomation has not yet been recognised as a reportable ailment in Malaysia, despite the fact that the Malaysian Health Informatics Center provides the total number of snakebites in the country. For example. from 2010 to 2014, a total of 15798 incidents of snakebites were recorded in the country. Over the same period, there were 16 fatalities, or an average of 3 to 4 fatalities each year. The states with the high rate of snakebites are Kedah and Perak, perhaps due to agricultural activity (Ghani, 2019). There are no statistics on the number of tragedies that is out of the healthcare facility's record.

The danger posed by nonvenomous or mildly venomous animals is frequently underestimated (Alirol, 2010). The great majority of snakes are non-venomous species, and they are frequently misidentified as dangerous snakes and blamed for snakebites in South Asia. *Coelognathus* species, for example, are huge, fast-moving snakes that are occasionally misidentified as cobras. Notably, several small snake species that are not venomous share the same colouring as kraits. Thus, identifying the major groups of poisonous snakes is critical for determining whether they are venomous and how their venom affects humans.

Literature Review

Properties of Snake Venom

Venom is sometimes thinner and nearly translucent in some snakes, kraits, and young of new species, however it frequently bears the previously observed yellow colour. Snake venom is a complex protein known as enzymes, of which only several enzymes are found in all snake venoms worldwide (Mara, 1996). Although no venomous snake carries all the enzymes, each one has a distinct function and effect (Freiberg, 2002). While certain enzymes aid in digestion, others are intended to paralyze its prey.

An enzyme called L-amino acid oxidase, which also helps with digestion and activates other enzymes, gives some vipers' venom a yellow tint. When hyaluronidase (found in many snake venoms) is present, other enzymes are absorbed by the victim more quickly. Proteinases, which are frequently found in the venoms of vipers, serve a crucial part in the digestive process of the snake by quickly degrading tissues. As it works to aid in the digestion of the flesh, this enzyme is one of those that severely damages human victims' tissue (Freiberg, 2002). The hemotoxin found in vipers can damage tissues, muscle structure, and others, leading to extensive scarring, gangrene, and irreversible loss of particular motor abilities (Mara, 1996). Adenosine triphosphatase is regarded to be one of the primary components that causes shock in the victim and functions as an immobiliser for smaller prey, and it is likely found in most snakes like vipers. Meanwhile, the deadliest species, especially elapids, contain cholinesterase, which attacks the nervous system and relaxes muscles to the point where the sufferer has little control. Elapids which include cobras and mambas, possess a far greater concentration of neurotoxic enzymes that impact the brain, central nervous system, and other organs. In addition, phosphodiesterase, which is also believed to be found in almost all venomous snakes, is responsible for the adverse cardiac reaction in victims as in a fast drop in blood pressure (Mara, 1996).

Classification and Effect of Snake Venom

Snake venoms can be categorised into those that affect the nervous system, blood, and tissues even though there are numerous unique toxins in each category and some toxins may have more than one harm. Additionally, snakes frequently carry a variety of toxic compounds in

various amounts. Depending on the snake species, its age, diet, and distribution, these poisons have different effects on prey.

Neurotoxins have the potential to kill or only induce mildly severe neuromuscular paralysis. Dizziness, headaches, and a loss of taste and smell are symptoms of neurotoxins, while pre-paralytic symptoms include increased sensitivity to sound and goosebumps (Pruksaphon, 2022). Examples include the short and long neurotoxins. They inhibit acetyl cholinesterase activity and the muscle nicotinic acetylcholine receptor, which tear cell membranes and destroy many cell types (Pruksaphon, 2022). For paralytic, ptosis (drooping eyelids), opthalmoplegia (double vision), flaccid facial paralysis (difficulty gringing, closing mouth and eyes tightly), paralysis of the tongue and mouth muscles increase salivation production but with inability to swallow (Shea, 2005). The paralysis of the diaphragm and other respiratory muscles raises the risk of inhalation and suffocation by causing saliva to accumulate at the back of the throat.

Coagulants is a reduction in the blood's ability to clot or coagulate which result in coagulopathy (incoagulable blood). Numerous chemicals found in snake venom affect the mammalian hemostatic system as either procoagulants or anticoagulants. These components interact with a number of the fibrinolytic pathway's and blood coagulation cascade's proteins (Tang, 2013). Circulating blood clots can cause thrombosis, with cerebral or pulmonary thrombosis or strokes being the most immediately fatal type if the body is unable to break them down.

Myotoxins cause rhabdomyolysis, which breaks down skeletal muscle, or paralyse the neuromuscular function, which causes damage to muscles, especially the respiratory muscles. One of the signs of myotoxins is myoglubinuria, which creates brown urine that is darker than hemoglobinuria when myoglobin, a pigment that delivers oxygen in muscles, flows into the urine (Shea, 2005). One of the most common components of venom that causes rhabdomyolysis is phospholipase A2, which is also responsible for presynaptic neurotoxic paralysis (Shea, 2005).

Hemotoxins that cause hemolytic illness can either cause direct lysis or indirect lysis due to erythrocyte lysis. It is one of the most common clinical signs in snakebite patients, particularly when viperid snakes bite. Indirect lysis requires the presence of phospholipids and is most likely caused by phospholipid hydrolysis products rupturing the cell membrane (Xie, 2020). Venoms that are hemotoxic may have negative effects on the heart and/or the blood vessels. A substantial reduction in blood pressure, which can be caused by a number of venom toxins, may be the most severe cardiovascular effect. Snake venom metalloproteinases, for example, produce hypotension indirectly by increasing vascular permeability through the destruction of capillary basement membranes, resulting in leakage and blood pressure reductions (Roberts, 2017) . Haemorrhagin is the component of snake venom responsible for hemorrhagic activity, and it is the leading cause of mortality in persons bitten by viperinae (Desmond, 2002). Early indicators of hemorrhagic stroke include bleeding gums or noses, bite sites, old scars, "first aid" wounds, ulcers, and blood in sputum, saliva, vomit, urine, or faeces (Shea, 2005). Sudden, severe headaches, stroke, shock, or stiff neck are all critical warning symptoms.

Cytotoxins cause necrosis, or tissue death, which is not immediately fatal. Although necrosis can appear anywhere on the body, it often does so near to the bite site. Gangrene and limb loss may occur if a finger, toe, hand, or foot are affected. Amputation, skin grafts, fasciotomies (massive surgical openings of tissue compartments in the bitten limb to relieve pressure on the blood vessels and other organs), and extended durations of recovery are possible treatments for injury. Cytotoxic snake bites may cause subsequent bacterial infections or the emergence of cancer (Shea, 2005).

Treatment of Snake Venom

Over time, numerous recommendations for treating a deadly snakebite have been made. Due to the quick spread of venom, the chance of secondary infection, and the lack of evidence that the practise is effective, the cut-and-suck technique is no longer advised. However, some authorities do not advocate using cryotherapy since they think it's ineffective (Freiberg, 2002).

Whenever possible, secure the snake's body to ensure accurate identification. The physician needs to be aware of how a venomous species caused the bite. In many parts of the world, it is also required to identify the species involved to deliver the appropriate antivenin, as simply looking for fang marks is not always enough. In addition, even though polyvalent antivenin which includes components for multiple species is available in some areas, viper antivenin will not work on a cobra bite and vice versa.

If a nonvenomous snake bites a victim, they may refuse antivenin because of the high possibility of a reaction to the horse from which it is derived. A doctor will conduct a skin or ocular reaction test to determine whether the patient is allergic before administering antivenin (Freiberg, 2002). Additionally, there is a tendency for increased sensitivity to repeated doses of venom and antivenin after taking antivenin. Even when antivenin has been given, bite-related injury to the nerves, blood vessels, or muscles frequently necessitates supportive care. Some snakes severely damage the flesh where they bite, leaving scars that are visible for years. No matter how small the bite, every fatal snake bite needs to be treated right away.

Additionally, there have been cases reported of people passing away after being bitten by non-lethal snakes due to heart attacks. Despite there being no snakes present, some people have died because they believed they had been beaten (Freiberg, 2002). Therefore, it's crucial not to terrify the patient. Many snakes' venoms are not 100% effective at the time of the bite, either because of poor strikes in which only one fang partially penetrates the victim due to partially empty glands (Freiberg, 2002).

Extraction of Snake Venom to Produce Antivenin

Since the 1950s, coagulants that act on fibrinogen have been identified as reptilase and agacutin (Tang, 2013). Reptilase, which is included in the venom of the *Bothrops jararaca* snake, is a coagulant that can be used effectively for therapeutic purposes. Due to its potential to shorten the time needed for blood to clot and bleed in vivo, it has been widely utilised to treat wound haemorrhages and to control bleeding during surgery. Many people are fascinated by the venom extraction technique because they cannot imagine snake venom serving any useful purpose. The toxins that bubble out from the glands of the snake have a variety of uses that man has found. These substances are used by doctors to study how the human body works and develop new treatments. Snake venom is used to create antivenin, a drug that mitigates the consequences of a snake bite.

The milking method is the most common, but far from the safest, method of obtaining venom. This entails taking the animal and inserting its fangs into the open mouth of a container, and then pressing on the venom glands if the snake does not release any venom readily. Today, many people use devices that deliver gentle electric shocks. In 1908 to 1962, venom was removed every 15 days from the reptiles while they were kept in an open serpentarium. A snake may survive for 15 days on average at this time. These snakes were moved to an altered building in 1963 for intensive care, which is now known as the Laboratory of Herpetology (LH) (Grego, 2021). The collecting containers have thin membranes enclosing the opening through which the fangs must pass. These are inserted to protect the extracted venoms from outside organisms and to give the animal the impression of

"making contact" with something, which stimulates venom production. Drying or deep freezing are used to preserve the venom. New snake venom quickly loses its effectiveness if not kept extremely cold. It loses virulence at room temperature and above in about 5 minutes, but at -200°C, it can be kept for up to 30 years, although a slight loss of virulence will happen (Mara, 1996).

Temperature has an effect on venom production in addition to how it affects venoms after they have been exposed to air. Dangerous snakes produce very little venom during the winter months, while production rises during the summer (Mara, 1996). This knowledge would be extremely helpful for those who depend on a consistent supply for their pharmaceutical demands.

The most popular process for producing antivenin is the horse serum approach. One-tenth to one-hundredth of a lethal dose of venom is administered to a horse. Typically at weekly intervals, the dosage is increased progressively until the animal can tolerate three to four times the initial dose. The serum of the antibodies is then separated from the animal's blood. Each and every antivenin is polyclonal, made up of combinations of antibodies produced in large mammals like horses against a variety of poisons in snake venom (Isbister, 2022). They are polyvalent if they are bred against numerous snake species or groups of snakes, frequently from different geographical locations, as opposed to monovalent if they are raised against just one type of snake. Monovalent antivenins have the advantage of being specific for a certain type of snake. As a result, they are smaller in size and contain less protein, reducing the risk of systemic hypersensitivity reactions. They won't work or will work less well if given to the wrong snake. Polyvalent antivenins lessen this problem, although they are bulkier and more likely to cause hypersensitivity reactions.

Both approaches are imperfect, though, as about one-third of individuals have negative reactions to horse serum. However, the death and morbidity brought on by envenomation typically outweigh any negative consequences of antivenin therapy. The bulk of reactions fall into two categories: type III immune complex reactions, which are characterised by serum sickness, and type I acute hypersensitivity reactions, which can be fatal (Otten, n.d.). It is essential to determine whether the patient is vulnerable to antivenin-related side effects and to be ready to provide the necessary treatment. Antihistamines and epinephrine can save a person's life in type I reactions, whereas steroids and antihistamines can treat type III reactions.

Conclusion

Snake venoms are categorised into three groups: those that affect the nervous system, blood, and tissues. However, there are many different toxins within each category, and some toxins may have more than one effect. Phospholipases A2 is one of the venom enzymes that can harm the vascular endothelium, erythrocytes, leukocytes, platelets, peripheral nerves, and skeletal muscle in addition to causing the production of inflammatory mediators. Antivenin is important because it inhibits or reverses envenomation in patients, effectively curing snake envenomation. Through the formation of immunocomplexes, it is an immunotherapy that binds to venom poisons, rendering them inactive and hastening their clearance. This is especially important for hospital pharmacists and physicians who are responsible for administering antivenin to envenomated patients.

Ethics Statement

The research does not require research ethics approval.

Authors Contribution

Original draft preparation - Ana Nurnasuha Mohd Nor; Literature Review, Writing - Ana Nurnasuha Mohd Nor, Farah Ayuni Farinordin; Review and editing - Nur Amalina Mohd Izam, Nor Azliza Ismail.

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Conflict of interests

The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

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