Update in
Anaesthesia

Management of snake envenomation

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Summary

Snake bites are common in many areas of the world and may be fatal. The common types of venomous snake are described, along with guidance on differentiation of bites by clinical presentation.

INTRODUCTION

Out of more than 3000 species of snake identifiable world wide, only one tenth of them are dangerous to human beings. There are three major families of venomous snakes:

Elapidae (Land snakes like cobra, krait and coral snakes)

Snakes of this family have short, fixed fangs, which contain venom channels. Their tricolour bands (black, red and yellow/white) encircle the body and they lack laureal shields (the shield on the lateral aspect of head separating those shields bordering the eyes from those bordering the nostril).

Viperidae (Russell's viper, bamboo snakes)

These are further classified into pit vipers (crotalinae) and viperine vipers (viperinae). Their fangs are long and movable. Their pupils are vertically elliptical. The ventral plates, caudal to anus, are in a single row. These snakes have a heat sensing pit as a small depression on the side of head for location of prey.

Hydrophiladae (Sea snakes)

These snakes have a flattened tail.

EPIDEMIOLOGY

Although a major public health problem in many countries the epidemiology of snakebite is still fragmentary, mainly due to lack of statistical data. This is compounded by the fact that the majority of victims come from rural areas, out of reach of available medical facilities. It is estimated that snakebites may exceed 5 million per year, out of which approximately 100 000 develop severe sequelae. The incidence also shows a distinct seasonal pattern, with a higher frequency in summer and during rains when the reptiles come out of their shelters. Epidemics of snake bite following floods, as human and snake populations are concentrated together, have been noted in Pakistan, India and Bangladesh.

Snakebite is observed in all age groups, the majority (90%) affecting 11 to 50-year-olds with males affected twice as often as females. Most bites occur between midnight and early morning and a large number of

Table 1. *Medically important snakes.*

Region	Types
North America	Eastern Diamond Rattlesnake (*Crotalus adamanteus*), Western diamond rattlesnake (*C. atrox, C. viridis*), Bothrops atrox (*fer-de-lance*)
Central and South America	Bothrops jararaca & tropical rattlesnake (*C. durissus, C. terrificus*)
Britain	European adder (*Vipera berus*)
Europe	Long nosed viper (*V. ammodytes*)
Africa	Night adder (Causus species), Puff adder (*Bitis arientan*), Mambas (four species of Dendroaspis)
Africa and Asia	Cobra (Naja species), Saw-scaled viper (*Echis carinatus*)
Part of Asia	Russell's viper (*V. russelli*) Malayan Pit viper (*Agkistrodon rhodstoma*) Sharp-nosed pit viper (*A. acutus*) Mamushi Pit viper (*A. halys*) Haliu viper (*Trimeresurus flavoviridis*) Kraits (*Bungarus coeruleus, B. multicinctus*)
Pacific-Australian area	Tiger snake (*Notechis scutatus*) Death adder (*Acanthophis antarcticus*) Taipan (*Oxyuranus scutellatus*) Papuan black snake (*Pseudechis Papuanus*) King brown (*Pseudechis australis*)

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bites occur in fields, as most individuals are unable to spot the snake due to tall grass and crops. Fortunately every bite does not result in complete envenomation and more than half of victims escape without serious poisoning. However, if sufficient venom is injected during the bite to cause serious poisoning, the mortality can be high.

PATHOPHYSIOLOGY

Snake venom is a very complex chemical poison, containing multiple proteins and peptides, in addition to carbohydrates and metals, which exerts toxic and lethal effects on the skin and the hematological, nervous, respiratory and cardiovascular systems (Table 2). Different species have differing proportions of these agents. The picture may be further complicated by the release of endogenous mediators such as histamine, bradykinin and adenosine. Therefore snake venoms cannot be classified purely as 'neurotoxic' or 'cardiotoxic', although they may have a predominantly specific action. The effects may be conveniently, though arbitrarily, classified into vasculotoxic for vipers, neurotoxic for elapids and myotoxic for sea snakes.

Viper venom

This is primarily vasculotoxic. It causes rapidly developing swelling of the bitten part. Local necrosis is mainly ischaemic, as thrombosis blocks the local blood vessels and causes dry gangrene. Systemic absorption is via the lymphatics. Some vipers such as *Vipera berus* (European Viper) cause vomiting, abdominal pain, explosive diarrhoea and shock within a few minutes of the bite, which resolves spontaneously within half an hour. Persistence of shock may however be fatal. Several viper venoms result in intracranial haemorrhage due to direct endothelial damage by 'haemorrhagin' (a venom component), which interestingly does not affect coagulation. In contrast other viper venoms (Crotalus, Bothrops) do affect coagulation and a very small amount of venom can cause complete fibrinogen consumption. This feature can also differentiate various species of vipers, which can help in instituting appropriate antivenom therapy.

Elapid venom

Local necrosis causes a picture like 'wet gangrene' with a characteristic putrid smell due to direct cytolytic action of the venom. Systemic absorption occurs through venous channels. These result in primarily neurotoxic features, causing selective neuromuscular blockade of the muscles of the eyes, tongue, throat and chest leading to respiratory failure in severe poisoning.

Sea snake venom

The effects are both myotoxic and neurotoxic, resulting in clinical and pathological changes typical of segmental myopathic lesions in skeletal muscles. Muscle pains may be last for several months unless treated.

CLINICAL FEATURES OF SNAKEBITE

The clinical presentation of a snakebite victim varies with the size and species of snake, the number and location of bites, and the quantity of venom injected. As many 30% of Pit viper bites and 50% of elapid bites result in no envenomation, sometimes referred to as 'dry bites'. The venom channel is recessed above the tip of the fang and the venom injected may be reduced by poor penetration or glancing blows, causing venom to be lost over skin and clothing. The volume of the venom available to a particular snake may also be reduced by previous bites. The age and health of the victim are also important determinants in the clinical presentation. However, whether the snake is poisonous or non-poisonous and regardless of the venom injected, the commonest symptom following snakebite is fright, which may lead to a vasovagal episode (faint).

Usually the minority of victims who receive a venom dose large enough to cause systemic poisoning will already have signs of this by the time they seek medical help. Differentiation of viperine from elapid systemic poisoning is usually obvious from simple clinical evaluation. A persistent bloody ooze from the fang marks may suggest the presence of snake venom anticoagulant. In difficult cases the presence of pain out of proportion to the size of the wound suggests snake envenomation whereas mild pain is more normally caused non-venomous snakes, anthropod bites (centipedes, spiders), bacterial fascilitis or myonecrosis.

Local manifestations

After envenomation, local swelling starts within few minutes. Fang marks may be difficult to see. Local pain with radiation and tenderness and a small reddish wheal are first to develop, followed by oedema, swelling and the appearance of bullae, all of which can progress quite rapidly and extensively. In most viper bites paraesthesia commences around the wound, and tingling and numbness over the tongue,

Table 2. *Snake venom components and their effects.*

Component	Pit viper	Coral snake	Effect
Enzymes			
Proteinases	Heavy	Minimal	Tissue destruction, coagulation, anticoagulation
Hyaluronidase	Moderate	Moderate	Hydrolysis of connective tissue stroma
Cholinestrase	Minimal	Heavy	Catalyzes hydrolysis of acetylcholine
PhospholipaseA	Heavy		Haemolysis may potentiate neurotoxins
Phosphomesterase	Minimal	Heavy	Unknown
Phosphodisterase	Moderate	Moderate	Hypotension
Non-enzymes			
Neurotoxins	Minimal	Heavy	Flaccid paralysis

mouth and scalp may follow. The local bite may become necrosed and gangrenous. Russell's viper has been reported to cause Raynaud's phenomenon and gangrene in a limb other than the one bitten. Secondary infection including tetanus and gas gangrene can also result. Since the venoms are largely absorbed by the lymphatics, lymphangitis may appear early. Petechiae or purpura may also be present due to the anticoagulant effect of some venoms. These characteristic changes are useful clinically - for example, if after a known Crotalid bite the victim demonstrates no local changes over several hours of observation, he can be released from the hospital as significant envenomation is unlikely.

In contrast Elapid snakebites are associated with minimal local changes.

Systemic manifestations

Cobra and vipers produce symptoms within a few minutes to several hours after the bite. Sea snake bites almost always produce myotoxic features with 2 hours, so that the bite can be reliably excluded if no symptoms are evident within this period. Although snakes are classified into predominantly neurotoxic, hemorrahagic and myotoxic types on the basis of their venoms, each species can result in any kind of manifestations.

Viper bites

75% cause envenomation, 35% mild, 15% severe. Pit viper venom can involve virtually every organ system. Nausea and vomiting are common and, if present early, suggest severe envenomation. Weakness, sweating, fever, chills, dizziness and syncope may occur. Some patients complain of a minty, rubbery or metallic taste in their mouths with increased salivation. Tingling or numbness in the tongue, scalp, face and digits are indications of moderate to severe envenomation, as are fasciculations of the face, neck, back or the bitten extremity. Systemic anticoagulation can lead to gingival bleeding, epistaxis, haemoptysis, haematuria, haemetemesis and rectal bleeding or malena. Intra-abdominal or intracranial haemorrhages may occur. Visual disturbances may result from retinal haemorrhages. There may be tachycardia or bradycardia, often accompanied by hypotension. Delayed shock may occur due to excessive blood loss and haemolysis. Severe envenomation can result in pulmonary oedema as a result of destruction of the intimal lining of the pulmonary blood vessels and pooling of the pulmonary blood. The venom itself and associated hypotension along with haemoglobin, myoglobin and fibrin deposition in renal tubules, can contribute to nephrotoxicity.

Elapid bites

The venom of elapid bites is primarily neurotoxic. Neurotoxic features are a result of selective d-tubocurarine like neuromuscular blockade, which results in flaccid paralysis of muscles. Ptosis is the earliest manifestation of cranial nerve dysfunction followed closely by double vision. Paralysis usually then progresses to involve the muscles of swallowing, but not strictly in that order.

Generally muscles innervated by cranial nerves are involved earlier. However the pupils are reactive to light until the terminal stages. The muscles of the chest are involved relatively late, with the diaphragm being most resistant. Respiratory paralysis is therefore often a terminal event. Even prior to respiratory failure, airway obstruction due to vomit or secretions can result in sudden death.

Reflex activity is generally not affected and deep tendon jerks are preserved until late. Symptoms that suggest severe envenomation include repeated vomiting, blurred vision, paraesthesiae around the mouth and hyperacusis (increased sensitivity to sound), headache, dizziness, vertigo and signs of autonomic hyperactivity. Tachycardia, hypotension and ECG changes may occur. Tetanic contraction of heart following a large dose of cobra venom has also been documented.

Sea snakes

Muscle pain is the most common presentation. Muscle necrosis may result in myoglobinuria and severe sea snake poisoning causes myoglobinuria and respiratory failure within a few hours. Coagulopathy is not a feature of coral snake bites.

In severe systemic poisoning following either elapid or viper bites, the electrocardiogram may show T-wave inversion and ST segment deviation. In sea snake bites, an ECG is especially valuable in detecting hyperkalemia, which can result from damage to muscles. Tall, peaked T-waves in the chest leads may appear within a few hours of bite and give early warning of impending death or acute kidney injury.

Unusual presentations of snake envenomation

- *Naja nigricollis* (spitting cobra) can eject venom from a distance of 6-12 feet. The venom is aimed at victim's eyes resulting in conjuctivitis and corneal ulceration. It may also cause anterior uveitis and hypopyon. A dull headache may persist beyond 72 hours.
- Occasionally a recently killed snake or snakes with severed heads can eject venom into those handling them.
- Rarely recurrence of snake envenomation manifestations may occur hours or even days after an initial good response to the antivenom. This may be due to ongoing absorption of the venom.

MANAGEMENT OF SNAKE BITE

The management of snake envenomation is controversial. It can be divided into first aid and prehospital care, specific antivenom therapy and supportive therapy.

First aid and prehospital care

Reassurance and immobilisation of the affected limb, with prompt transfer to a hospital are of prime importance. The application of a 'constriction band' to delay absorption and venom spread has been advocated during transit to hospital for bites to a limb. A firm, but not tight, ligature may be applied just above the bite. The tension is correct if one finger can pass between the limb and the bandage. This will impede lymphatic drainage, but not arterial or deep venous flow. It should preferably not be released until the administration of anti-snake venom. If the limb becomes oedematous the band should be advanced proximally. However, the band should not be left in place for too long, due to the risk of venous thrombo-embolism and distal ischaemia. An increase in local envenomation has also been reported subsequent to release of the band. Venous or arterial tourniquets are contraindicated.

The site of the bite should be cleaned and covered with a handkerchief

or dressing. Incision and mechanical suction of the bite (intended to open the puncture wound so that suction can be more effective) may be beneficial when performed by a health care worker within a few minutes of the bite, in a victim who is more than 30 to 60 minutes from hospital. The incision should be parallel to the axis of the extremity and should be only approximately 6 mm long and 3mm deep and cross cuts or multiple cuts should be avoided.

Mechanical suction (e.g. the'extractor' device found in a Sawyer first aid kit) is preferable to mouth suction, in order to avoid wound contamination with oral flora and to prevent possible envenomation of the rescuer through breaks in their oral mucosa. Suction should be maintained for about 30-60 minutes for maximal benefit, but due care should be taken as laceration of nerves, tendons and vessels has been reported following suction by untrained rescuers.

Application of cooling measures such as ice packs or cryotherapy, at the site of bite were initially advocated, but have not been proven to be effective and this practice is not now recommended.

Antitetanus toxoid should always be given following snakebite. There is controversy about use of drugs as part of first aid care. It has been suggested that NSAIDS may be beneficial to relieve local pain but may precipitate bleeding, especially if the venom is vasculotoxic. Paracetamol and/or codeine may be useful, however there are no clear-cut recommendations for the use of sedatives.

If the snake has been killed, it should be taken to hospital, otherwise it should be left alone, since attempts to find or kill it may result in further bites. The snake, even if judged to be dead, should be handled very carefully, since decapitated heads can bite for up to one hour!

Patient assessment

Evaluation should begin with the assessment of the airway, breathing and circulatory status. Oxygen should be administered to every envenomated patient and a large bore intravenous line with normal saline or Ringer's lactate established in the unbitten limb. Cardiac monitoring and pulse oximetry, if available, is indicated. Attempts should be made to determine whether a venomous snake has actually bitten the patient, and the severity of envenomation should be assessed. (Table 3)

During the initial evaluation, several locations on the bitten extremity (at the bite site and at least two sites more proximal) should be marked and the circumferences should be measured every 15 minutes until swelling is no longer progressing and every 1-4 hours thereafter. The extremity should be placed in a well-padded splint for at least 24 hours.

Laboratory investigations

Although lab tests are of little value in the diagnosis of snake envenomation, nevertheless they are useful for monitoring the patient and deciding about specific interventions and prognosis. They should include a full blood count, electrolytes, glucose, creatinine, serum amylase, creatinine phosphokinase (CPK), prothombin time (PT), partial thromboplastin time (PTT), fibrinogen and fibrin degradation products (FDPs). Commonly hyperkalaemia and hypoxaemia with respiratory acidosis may be seen, particularly with neuroparalysis. Urine examination may reveal haematuria, proteinuria, haemoglobinuria or myoglobinuria. Arterial blood gases and urine examination should be repeated at frequent intervals during the acute phase to assess progressive systemic toxicity.

Blood changes include anaemia, lecuocytosis (raised white cell count) and thrombocytopenia (low platelet count). The peripheral blood film may show evidence of haemolysis, especially in viperine bites. Clotting time and prothrombin time may be prolonged and a low fibrinogen may be present. Blood should be typed and crossmatched on the first blood drawn from the patient, as both direct venom and antivenom effects can interfere with later crossmatching. Some specialised centers can identify the species of snake involved.

Non specific ECG changes such as bradycardia and atrioventricular block with ST and T segment changes may be seen.

Recently electroencephalgram (EEG) changes have also been reported in many patients of snake envenomation. They may manifest within hours of bite without any clinical features suggestive of encephalopathy.

Antivenom therapy

Anti snake venoms (ASV) are prepared by immunising horses with venom from poisonous snakes, extracting serum and purifying it. The WHO has designated the Liverpool School of Tropical Medicine as the international collaborating center for antivenom production and testing. Antivenoms may be species specific (monovalent) or effective against several species (polyvalent) (Table 4).

The correct use of antivenom is the most important component of hospital care and not every bite, even with a poisonous snake, merits its use. Administration of antivenom should be selective and based

Table 3. *Assessment of severity of envenomation.*

No envenomation	Absence of local or systemic reactions. Fang marks +/-
Mild envenomation	Fang marks. Moderate pain, minimal local oedema (0-15cm), erythema +, ecchymosis +/-, no systemic reactions
Moderate envenomation	Fang marks +, severe pain, moderate local oedema (15-30cm), erythema and ecchymosis +, systemic weakness, sweating, syncope, nausea, vomiting, anaemia or thrombocytopenia
Severe envenomation	Fang marks +, severe pain, severe local oedema (>30cm), erythema and ecchymosis +, hypotension, parasthesia, coma, pulmonary oedema, respiratory failure

on the severity of clinical symptoms. The main concern about the empirical use of antivenom is the risk of allergic reactions, its relative scarcity in some centers and the cost. Moreover, in a study of Elapid envenomation, all victims with neuromuscular paralysis survived without receiving any antivenom. Shemesh et al did a preliminary evaluation of the possibility of reducing the dose of anti-venom or totally avoiding it in some viper species.[9] They concluded that about half of bitten patients in their study did not show systemic symptoms and therefore did not require antivenom treatment. They further observed that antivenom treatment based on systemic symptoms was effective and the dose required was also less than the fixed amount advocated for each patient, thereby reducing the incidence of serum sickness.

Administration of antivenom

Antivenom should be given within 4-6 hours of the bite and the dosage required varies with the degree of envenomation. Serum sensitivity should be tested by injecting 0.2ml of antivenom subcutaneously. If a severe reaction occur within 15 minutes, antivenom is contra-indicated. Epinephrine should be readily available in a syringe for moderate reactions that may occur despite negative tests for sensitivity.

The initial dose should depend upon an estimate of amount of envenomation (Table 5). However no upper limit has been described and up to 45 vials have been successfully used in a patient. In children and small adults (body weight < 40kg) up to 50% higher dose of ASV should be administered, to neutralise the relatively higher venom concentration.

ASV is administered intravenously, either in an undiluted form at a rate of not more than 1ml per minute, or diluted in 500ml of IV fluid and administered as rapidly as tolerated over 1-2 hours. Additional infusions containing 5-10 vials (50-100ml) should be repeated until progression of swelling in the bitten part ceases and systemic signs and symptoms disappear. However it is not advisable to infiltrate ASV at the local site. Delayed reactions may occur following anti-venom therapy and their frequency of occurrence is proportional to the amount of antivenom administered. Therefore all patients receiving ASV should be observed for several days.

Role of anticholinesterase agents

Since Elapidae snakes result in primarily neurotoxic features as a result of selective d-tubocurarine like blockade, the post-synaptic toxin of the venom leads to pathophysiological changes resembling those of myasthenia gravis. This prompted use of anticholinesterase agents, such as neostigmine, in addition to a conventional antivenom therapeutic regimen with dramatic results. However the use of anticholinesterase drugs alone, without ASV, has also been recommended.

Table 5. *Dose of antivenom.*

Envenomation	Dose
Mild	5 vials (50ml)
Moderate	5-10 vials (50-100ml)
Severe	10-20 vials (100-200ml) or more

Neostigmine can be given as 50-100mcg.kg^{-1} 4 hourly or as a continuous infusion. Edrophonium can also be used in dose of 10mg in adult or 0.25mg.kg^{-1} in children over 2 minutes. If the response is positive then one can switch over to long acting preparations like neostigmine. However prospective studies are required to fully establish the efficacy of neostigmine with or without ASV. Glycopyrrolate 0.2mg preceding neostigmine can be given, as unlike atropine it does not cross blood brain barrier.

Table 4. *Types of antivenom.*

Name of Antivenom	Species
Polyvalent Wyeth Labs [Antivenin (cortalidae) polyvenom] United States	All North American pit vipers
King cobra antivenom	King cobra *(Ophiophagus hannah*)
Polyvalent Naja naja serum (common cobra) antisnake venom CRI, Kausali, India	*Vipra russelli* (Russell's viper) *Bungarus ceruleus* (common krait) *Echis carinatus* (saw scaled viper)
Mono specific Echis carinatus antivenom, India	Indian species
Tiger snake antivenom, Australia	Sea snakebite & Afro-Asian elapids
Green pit viper antivenom	*Trimeresurus albolabris, Trimeresurus monticola*
Bothrops antivenoms, Brazil	
Monospecific antivenom from South African Institute for Medical Areas (SAIMR), Northern Nigeria	*Echis pyramidum leakeyi*
Poly specific German & French antivenoms	

Storage of ASV: Liquid -between +20 & +80C, Lyophilized - cool & dry place.

Supportive therapy

The patient should be moved to an appropriate area of the hospital - ICU will be required for severe envenomation. Fasciotomy should be undertaken in patients with compartment syndrome and debridement should be performed for necrotic tissue. Coagulopathy should be corrected with fresh frozen plasma and platelets. Blood transfusion should be given to replace blood loss from haemolysis and bleeding. Ventilatory support and haemodialysis may be necessary for pulmonary and renal complications, due to severe envenomation. Corticosteroids are of no proven value and in fact may interfere with the action of ASV. However, corticosteroids may be used for hypersensitivity reactions to ASV. Prophylactic antibiotics are of no proven value. If infection occurs broad spectrum cover, such as ciprofloxacin and clindamycin, should be used.

Intravenous immunoglobin therapy has also been used for envenomation and it may improve coagulopathy, but has no effect on neurotoxicity. Certain reports on the evaluation of intravenous immunoglobin suggest that it may reduce the need for repeat antivenom therapy for envenomations associated with coagulopathy.

A compound (2-hydroxy 4-methoxy benzoic acid) isolated and purified from anatamul (*Hemidesmus indicus*), an Indian herb, has also been observed to have potent anti-inflammatory, antipyretic and antioxidant properties, especially against Russell's viper venom.

Analgesia should be given - opioids may be required.

OTHER ENVENOMATIONS

Scorpion venom poisoning

There are more than 1,400 species of scorpion in the world, but the number of medically important species is limited. The venom of the Bark scorpion (*C. exilicauda*) contains at least five distinct neurotoxins that stimulate depolarization of the neuromuscular junction and autonomic nervous system, via release of acetylcholine, norepineprine and epinephrine. It may also have cardiotoxic effects.

Most stings are minor although serious envenomations can occur in children. The sting is followed by the onset of intense local pain with hyperesthesia (increased skin sensitivity to touch) but local swelling and ecchymosis are absent. Systemic symptoms, when present, reflect sympathetic, parasympathetic and neuromuscular excitation. Tachypnoea, respiratory distress, wheezing, stridor, muscle fasciculations and spasm follow initial restlessness and anxiety. There may be convulsions, paralysis and involuntary voiding of stools/urine, priapism (persistent penile erection) and anxiety. Other systemic features may include hypertension, supraventricular tachycardia and hyperpyrexia.

The majority of stings can be treated with mild analgesics and cold compresses. In the event of severe envenomatiom, the patient should be resuscitated and appropriate symptomatic treatment should be instituted. A goat-derived antivenom is available in Arizona. Most adults can be safely treated at home, but children should always be admitted and any child less than a year old, or with neurological findings, should be admitted to ICU.

FURTHER READING

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