SNAKES AND SNAKE BITES – Part 2: Venoms and Antivenoms

Moses Chisale, Regional Advisor Pharmaceuticals, WHO Regional Office for Africa, Brazzaville, Republic of Congo

1. Introduction

In the last issue of the AFRO Pharmaceuticals Newsletter (Volume 4, No.1, July 2007), we discussed the prevention of snakebites. We looked at the rather difficult co-existence between humans and snakes, the distribution of snakes in the African Region, ways of preventing snake bites, the first important things that need to be done (first aid) and to be avoided in case of snake bite, and some traditional aspects of snakes and snake bites.

We also announced that future editions of the newsletter would deal with venoms and antivenoms, as well as some important clinical syndromes resulting from snake bites. In this newsletter, we look at the composition of snake venoms, their effects on the body and the clinical profiles of envenoming by some snakes of medical importance. We also discuss the production and use of antivenoms, as well as current WHO work on the subject.

The WHO Regional Office for Africa is currently developing Guidelines for the Prevention and Clinical Management of Snake Bites. These Guidelines are expected to be released in 2008. More detailed information on the issues discussed in the newsletter will be included in those guidelines.

2. Identification of venomous snakes

Some venomous dangerous snakes can be easily identified by their size, shape, color, pattern of markings, behavior and the sound they make when they feel threatened (e.g. defensive behavior of the cobra: hood, hissing, repeated strikes towards aggressor). However, there is no simple rule for identifying them. In addition, some harmless snakes have evolved to look almost like venomous snakes.

3. Snake venoms

The primary function of snake venoms is to help the snake immobilize and eventually digest its prey. Snake venoms are complex compounds containing numerous components, mainly proteins. The most important venom components that lead to significant clinical effects after a bite are enzymes and polypeptide toxins.

With contributions from Sanda Ashe (Watamu Snake Farm, Watamu, Kenya) and Jean-Philippe Chippaux (IRD, La Paz, Bolivia).
The amount of venom injected during a bite depends on various factors: species and size of the snake, mechanical efficiency of the bite, whether one or two fangs penetrated the skin, and whether there were repeated bites. For some reason, not all bites by venomous snakes lead to venom injection (dry bites). Even after several bites or after eating their prey, snakes do not exhaust their venom, and they remain just as venomous.

It is, however, very important to realize that even in the case of dry bites or when people suspect or simply imagine that they have been bitten by a snake, they can develop some signs due to extreme anxiety: over-breathing, stiffness or dizziness, agitation, or shock with profound slowing of the heart.

Within the same species, larger snakes will also tend to inject more venom than smaller ones, but the venom of the latter may be richer in some very dangerous components. Bites by small snakes should therefore not be neglected but should receive the same attention as those by larger snakes.

4. Snake venom components
The most important venom components that cause serious clinical effects are pro-coagulant enzymes, cytolytic or necrotic toxins, hemolytic and myolytic phospholipases A₂, pre- and post-synaptic neurotoxins, and haemorrhagins.

Pro-coagulant enzymes are mainly found in vipers. They activate different steps of the blood-clotting cascade. This leads to the formation of fibrin in the blood. Most of the fibrin is broken down by the body’s fibrinolytic system. This process depletes the body’s own levels of clotting factors, and eventually the blood does not clot. This is also called consumption coagulopathy.

Cytolytic or necrotic toxins are digestive hydrolases (proteolytic enzymes and phospholipases) that may destroy cell membranes and tissues and therefore increase the permeability of the vascular endothelium. This leads to local swelling, blistering and oedema.

Hemolytic and myolytic phospholipases A₂ damage cell membranes, endothelium, skeletal muscle, nerves and red blood cells.

Pre-synaptic neurotoxins are mainly found in elapid venoms, but they are also found in some vipers. They are phospholipases A₂ that damage nerve endings, initially releasing acetylcholine followed by interfering with its release.

Post-synaptic neurotoxins are mainly found in elapid venoms. They are polypeptides that compete with acetylcholine for neuromuscular junction receptors and lead to curare-like paralysis.

Haemorrhagins are zinc metalloproteinases that damage the endothelial lining of blood vessel walls causing spontaneous local and systemic hemorrhage.

5. Snake bite classification
Very broadly, the above described venom components can lead to three types of symptoms or bite types as discussed below.

Cytotoxic bites are characterized by painful and progressive swelling with watery blood leaking from the bite wound, shock, blistering and discoloration. The victim will complain of severe pain at bite site and affected limb. Species involved with this type of bite include puff adder, Gaboon adder and spitting cobras.

Neurotoxic bites are characterized by moderate swelling, cold and clammy feet, dilated pupils, drooping eyelids and aching joints. The patient complains that the skin is twitching, has swollen lymph glands, vomits, has heavy salivation and breathing difficulties, feels weak or paralyzed. Species involved with this type of bite include black and green mambas and non-spitting cobras.

Hematotoxic bites are characterized by bloody gums, nose, corner of eyes, and bleeding from scratches and old wounds. Species involved include Boomslang and vine snake.

There are also some mixed symptoms. Mixed cytotoxic and neurotoxic bites can occur in the case of Rinkhals cobra and most other spitting cobras. Mixed Hematotoxic and cytotoxic bites result from carpet vipers, North African desert vipers and puff adders, especially Bitis arietans.

6. Snake bite in children and the elderly
Children are more prone to morbidity and mortality due to the higher dose of venom they receive relative to their body weight compared to adults. However, the dose of antivenom to be administered is the same as for an adult. This is because the antivenom is designed to neutralize a fixed venom dose which the snake injects indiscriminately into humans large or small.

The elderly are similar to children when it comes to snake bite. They are, however, more prone to hypotension, therapeutic fluid overload and adverse effects of adrenaline (epinephrine). They are also more likely to be suffering from other unrelated chronic illnesses such as hypertension, other cardiovascular diseases, chronic obstructive bronchitis and diabetes mellitus.

7. Snake venom in the eyes
There are eight spitting elapid species in the African Region, including the Mozambican cobra (Naja mossambica) but excluding the Egyptian cobra (Naja haje). They are capable of spitting their venom into the eyes of a victim leading to intense pain in the eyes. This may lead to intense conjunctivitis, corneal erosions, and red blood cells.

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1 Sanda Ashe (2004), Primary Medical Care of Snake bites, p 2, Bio-ken Snake Farm and James Ashe Antivenom Trust.
2 See also Roger Blaylock’s algorithm on the management of snake bite to be included in the forthcoming AFRO Guidelines for the Prevention and Clinical Management of Snake Bites (in production).
complicated by secondary infection, anterior uveitis and sometimes blindness.

First aid treatment consists of abundantly irrigating the eye with water or if possible normal saline. A single application of local anesthetic eye drops helps to overcome tightly closed eyelids and facilitates irrigation. Topical or systemic antivenom treatment is not indicated. Steroids (topical or systemic) are contraindicated. The patient should be treated as for a corneal injury with a topical antimicrobial agent (tetracycline and chloramphenicol). Adrenaline eye drops (1:1000) are said to relieve the burning sensation instantaneously.

8. Snakebite in pregnancy

Snake bite in early pregnancy may lead to teratogenesis. Envenoming by saw-scaled or other vipers that cause bleeding may precipitate miscarriage at any stage of pregnancy. Pregnant women should be questioned about and examined for evidence of vaginal bleeding and, in the third trimester, fetal heart rate, and uterine contractions should be monitored.

Envenomed pregnant women are at risk of ante- and post-partum hemorrhage, premature labour, fetal distress and stillbirth. Early adequate antivenom treatment is indicated, its benefits outweighing the risks to the mother and fetus of anaphylactic antivenom reactions.

9. Antivenoms

Antivenom (also known as antivenom immunoglobulin, antivenin, anti-snake bite serum and snake bite antiserum) is the only effective treatment for snake bite envenoming from a deadly snake if it is given in sufficient quantities and in time.

Antivenom is prepared from animals (most often horses, but also donkeys or sheep) hyper-immunized against the venom(s) of snakes whose bites lead to severe envenoming in the geographical area where the particular antivenom is to be used. The venom of a single species of snake may vary, in composition and anti-genicity, with the age of the snake, season of the year and throughout the species’ geographical range (“intra-species” variation in composition).4 Pooled venom from many individual specimens of each species may therefore be used for antivenom production. They should come from different parts of the geographical range and should include some younger (smaller) specimens.

After animals have completed the immunization schedule, plasma is collected and passed through several processes designed to produce either refined whole IgG antibodies or IgG antibody fragments such as F(ab’)_2 or Fab, which are free of other plasma proteins such as albumin, aggregates, pyrogens and microbes, some of which are responsible for antivenom reactions. It is then either lyophilized or stored as a liquid.

Poly-specific (also known as polyvalent) antivenom is derived from animals hyper-immunized against the venoms of several snake species, while mono-specific (monovalent) antivenom is derived from animals immunized against the venom of a single snake species. Poly-specific antivenom allows syndromic management of snake bite where the identity of the snake responsible for the bite is uncertain.

Mono-specific antivenom requires precise knowledge of the snake species responsible. It is therefore necessary that, if possible, the snake responsible for a bite be brought forward to the health facility for proper identification. However, very few medical doctors and nurses are capable of identifying snakes; this underscores the need for training and information for health workers, particularly those in high-risk areas.

Lyophilized antivenom powder has a longer shelf-life but is more expensive than liquid antivenom and must be re-dissolved before use. Liquid antivenom in glass ampoules should be stored at 2°C to 8°C (not frozen). Care should be exercised before its use to ensure that it is clear and contains no visible particles, floccules or precipitate.

10. Antivenom treatment

Antivenom is the only specific antidote to snake venom. To be effective, antivenom should be produced using venom from snake species found in the geographical area where the antivenom will be used. Antivenom is also scarce and expensive. Production and supply of effective antivenom is still a big challenge in health facilities of most countries in the African Region. Where possible, it should be administered by a medically qualified person. Antivenom should never be used routinely and indiscriminately but only when indicated. Remember:

- Most antivenoms carry a risk of potentially dangerous early anaphylactic reactions.
- Antivenom is not always necessary: some patients are bitten by non-venomous snakes, and 10%–50% of those bitten by venomous snakes may not be envenomed.
- Antivenoms have a defined range of specific and para-specific neutralizing activity but are useless for venoms outside that range. Currently, specific antivenoms are not available for the treatment of envenoming by some species.
- Antivenom is very expensive and usually in short supply, particularly in Africa.

Warning: When patients arrive in hospital with a tourniquet or other constricting band in place, antivenom treatment, if necessary, should be given before these are loosened as there is a risk of severe envenoming when the venom in the occluded limb is released into general circulation.

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If the species responsible for the bite is known for certain, mono-specific antivenom, if available, is the optimal treatment. However, in areas where the venoms of a number of different species produce similar clinical effects, poly-specific antivenoms must be used in the majority of patients who do not bring the dead snake for identification. Poly-specific antivenoms can be just as effective as mono-specific antivenoms for the prescribed range of venoms which they cover and may be less expensive.

Antivenom is most effective when given intravenously. Freeze-dried (lyophilized) antivenom should re-dissolved quickly (less than 10 minutes) in sterile water. Antivenom can be given by intravenous injection at a rate of about 5 ml per minute, or diluted in isotonic fluid and infused over 30–60 minutes. The incidence and severity of antivenom reactions is the same with these two methods.

When intravenous administration is impossible, antivenom can be given by deep intramuscular injection at multiple sites in the anterior and lateral aspects of the thighs, followed by massage to promote absorption. This is not ideal and not generally recommended as absorption is very slow and there is a limit to the volume of antivenom that can be given by this route, with risk of haematoma formation in patients with incoagulable blood.

11. Antivenom dosage

Antivenom neutralizes a fixed amount of venom. Since snakes inject the same amount of venom into adults and children, the same dose or volume of antivenom must be administered to children as to adults.

Antivenom manufacturers provide some initial dosage recommendations in their package inserts. However, these are based on mouse assays which may not always correlate with clinical findings. In addition, the initial dose of antivenom, however large, may not completely neutralize the depot of venom at the site of injection or prevent redistribution of venom from the tissues.

Patients should therefore be observed for several days, even if they show a good clinical response to the initial dose of antivenom. Continuing absorption of venom from the bite-site depot and re-distribution of venom from the tissues may cause recurrent symptoms after therapeutic antivenom has been eliminated.

12. Antivenom reactions

Some patients receiving antivenom may develop a reaction within a few hours or some days later. It is therefore recommended that a syringe with epinephrine (adrenaline) be at hand for use in case of early anaphylactic reaction.

Early anaphylactic reactions may occur within minutes or hours of antivenom administration. The patient develops itching, urticaria, dry cough, fever, nausea, vomiting, abdominal colic, diarrhoea and tachycardia. In some severe cases there may be life-threatening conditions such as hypotension, bronchospasm and angio-oedema.

Pyrogen (endotoxin) reactions may also occur within 1 to 2 hours: shaking chills, fever, febrile convulsions, vasodilatation and fall in blood pressure. These reactions are caused by pyrogen contamination during the antivenom manufacturing process.

Late (serum sickness) reactions may develop within a week after treatment. Symptoms include fever, nausea, diarrhoea, vomiting, itching, arthralgia, myalgia, proteinuria.

There is however no absolute contraindication to antivenom treatment. Nevertheless, patients who have previously reacted to horse (equine) or sheep (ovine) serum in the past (equine anti-tetanus serum, equine anti-rabies serum) and those with a history of atopic diseases (especially severe asthma) should be given antivenom only if they have signs of systemic envenoming. The necessary precautions should be taken before, during and after the administration (adrenaline, antihistamines).

13. Antivenom production and supply

Today there are very few antivenom manufacturers in the world. In Africa, where the need is probably greatest, there are currently only three manufacturers in Egypt, South Africa and Tunisia. France and Mexico also produce some good antivenom for Africa. Some antivenom produced in other regions, particularly India, has been found in some African countries. These antivenoms have been marketed in Africa yet they may not be effective against African snake envenoming since Asian snake venoms are nearly always used in their production.

It is therefore urgent to promote international collaboration in the manufacture of sufficient quantities of effective, safe and affordable antivenoms and their distribution to areas of greatest need. Development of effective treatment protocols and training of medical personnel to implement them should also receive attention.

There is also need to improve knowledge of the epidemiology of snakes and snake bites, as well as the reporting of snake bites by medical facilities. It is essential to sensitize and educate the public on ways to prevent snake bites, identification of the dangerous snakes in their respective areas as well as on proper first aid methods in case of bite. The public, and in particular traditional healers, should be discouraged from using and promoting unproven remedies, especially when these are dangerous, e.g. incisions for the application of black stone and administration of herbs that may cause vomiting.


WHO (2005), Guidelines for the Clinical Management of Snakebites in the South East Asia Region. New Delhi, World Health Organization.