The role and use of antivenom in Cambodia

Lecture 8: Snake Bite Management Course

Introduction (1)

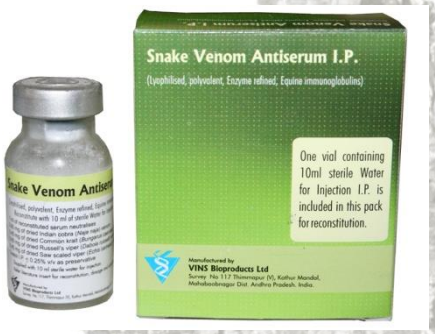
- The Cambodian Ministry of Health currently purchases a variety of imported Indian and Chinese antivenom products for distribution to hospitals.
- None of these products are appropriate for use in the treatment of snake bite envenoming caused by any of the medically important snake species that occur naturally in Cambodia.
- This is because none of these antivenoms are made from the venoms of snakes that occur in Cambodia
- Some of these products are also associated with very high adverse reaction rates

Introduction (2)

- This unfortunate situation arose in the wake of severe flooding along the Mekong River in 1997
- Incorrect advice was provided to the Cambodian Ministry of Health by the internet- based "*Global Health Disaster Network" (GHDNet)*
- The reasons for this error appears to have been an assumption by the Japanese and American advisors to GHDNet that Cambodia had the same snake fauna as India.
- Many thousands of US dollars have been wasted by purchasing the wrong antivenoms.

Antivenoms in use in Cambodia

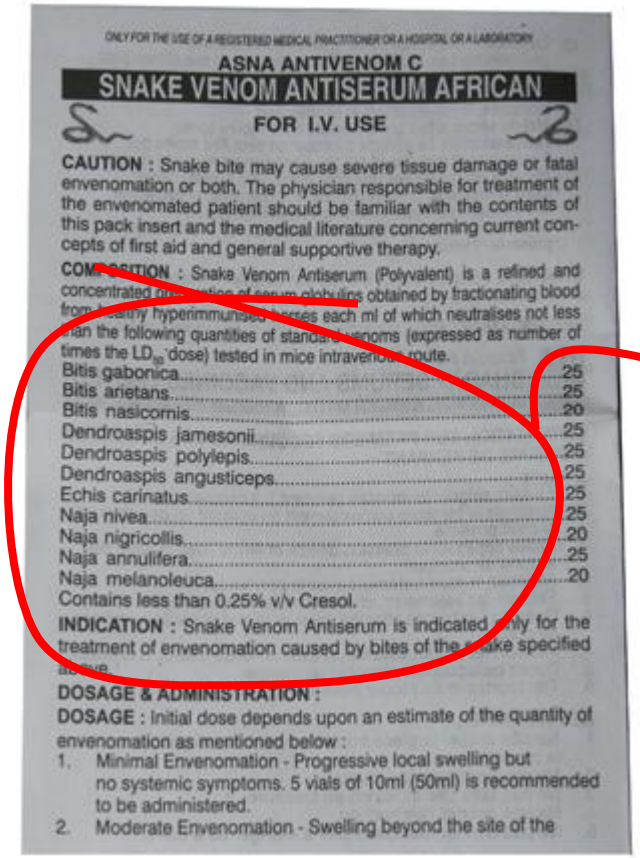
Four different Indian antivenoms that have been sold to the Ministry of Health in recent time



Several different antivenom products are in use, or have recently been used in Cambodia:

- **Snake Antivenin Polyvalent I.P.**
  - (Biological E Limited of India)
- **Snake Antivenom Serum I.P. SII Anti-snake Venom Serum**
  - (Serum Institute of India/Haffkine Biopharmaceutical Corporation of India)
- **ASNA Antivenom C: Snake Venom Antiserum African**
  - (Bharat Serums & Vaccines Limited of India)
- **Snake Venom Antiserum I.P.**
  - (VINS Bioproducts Ltd of India)
- **King Cobra Antivenom**
  - (Red Cross Society of Thailand)
- **Chinese Cobra Antiserum**
  - (Shanghai Institute of Biological Products from China)

Unscrupulous antivenom marketing



ONLY FOR THE USE OF A REGISTERED MEDICAL PRACTITIONER OR A HOSPITAL OR A LABORATORY

ASNA ANTIVENOM C

SNAKE VENOM ANTISERUM AFRICAN

FOR I.V. USE

CAUTION : Snake bite may cause severe tissue damage or fatal envenomation or both. The physician responsible for treatment of the envenomated patient should be familiar with the contents of this pack insert and the medical literature concerning current concepts of first aid and general supportive therapy.

COMPOSITION : Snake Venom Antiserum (Polyvalent) is a refined and concentrated [illegible] obtained by fractionating blood from healthy hyperimmunised horses each ml of which neutralises not less than the following quantities of standard venoms (expressed as number of times the LD_{50} dose) tested in mice intravenous route.

Bitis gabonica	25
Bitis arietans	25
Bitis nasicornis	20
Dendroaspis jamesonii	25
Dendroaspis polylepis	25
Dendroaspis angusticeps	25
Echis carinatus	25
Naja nivea	25
Naja nigricollis	20
Naja annulifera	25
Naja melanoleuca	20

Contains less than 0.25% v/v Cresol.

INDICATION : Snake Venom Antiserum is indicated only for the treatment of envenomation caused by bites of the snake specified above.

DOSAGE & ADMINISTRATION :

DOSAGE : Initial dose depends upon an estimate of the quantity of envenomation as mentioned below :

1. Minimal Envenomation - Progressive local swelling but no systemic symptoms. 5 vials of 10ml (50ml) is recommended to be administered.
2. Moderate Envenomation - Swelling beyond the site of the

- A number of Indian antivenom manufacturers have been shown to have marketed products in countries where they KNOW the products do not work.
- Bharat's ASNA Antivenom C is made from the venom of Indian and African snakes!
- No preclinical or clinical trials data has been published by the manufacturer
- In an independent study in Ghana, use of this product resulted in a 6-fold increase in the number of snake bite deaths

Unscrupulous antivenom marketing

Labels show that these products are made from Indian snake venoms for treatment of Indian snake bites!!

- Antivenoms made for use in the treatment of Indian snake bites:
  - Snake Antivenin Polyvalent I.P. made by Biological E Limited of India
  - Snake Antivenom Serum I.P. SII Anti-snake Venom Serum made by the Serum Institute of India/Haffkine Biopharmaceutical Corporation of India
  - Snake Venom Antiserum I.P. made by VINS Bioproducts Ltd of India
- Neither product is effective against the venom of Cambodian snake species
- Even against Indian snake species, very large doses are required
  - Some patients recieve more than 150 vials = **treatment failure**!!
- Adverse reaction rates up to 80%

Efficacy of Indian antivenoms

Species	Venom Yield	Antivenom Potency	Number of Vials Needed
Naja spp. (cobras)	58-742 mg	0.6 mg/mL	10-124
Bungarus spp. (kraits)	8-60 mg	0.45 mg/mL	2-14
Daboia spp. (Russell's vipers)	21-268 mg	0.6 mg/mL	4-45

- These are empirical antivenom volumes based on the range of venom yields produced by snake species
- In India the starting dose for these antivenoms is a minimum of 10 vials, but clinical data suggests that these antivenom often fail
- Several published studies show that very high doses may be given without significant clinical improvement
  - An Indian study of elapid snake bites reported an average of 51.2 vials (range: 5-190 vials)
  - A study of viper bites used an average of 32 vials (range: 1-130 vials)

Suitability of different Indian-made antivenoms for use in Cambodia

- No Indian-made antivenom product has been subjected either to preclinical assessment against venoms from Cambodian species
- No Indian-made antivenom product has been subject to any clinical trial to establish safety and efficacy in the treatment of snake bite by any of Cambodia's snake species
- These products are not clinically suitable for use in the treatment of snake bite in Cambodia
- The use of these products is potentially dangerous to patients due to high adverse reaction rates

Other imported antivenoms

- **King Cobra Antivenom** (Thai Red Cross Society):
  - Only suitable for treatment of king cobra bites, which are very rare
  - May have some polyspecific coverage against other cobra bites, but there is no published data to demonstrate this
- **Chinese Cobra Antiserum** (Shanghai Institute of Biological Products):
  - May be suitable for bites by Cambodian cobras, but there is no published data to demonstrate this
- Neither of these antivenoms would be suitable for bites by pit vipers, kraits or seasnakes

Antivenoms that are suitable for use in the treatment of snake bite in Cambodia

Monocellate cobra
Indo-Chinese spitting cobra
King cobra
Malayan krait
Banded krait

Malayan pit viper
Indo-Chinese Russell's viper
Green pit vipers

- Thailand shares the same snake species as Cambodia
- Thai Red Cross Society make antivenoms that are suitable for use in Cambodia
  - **TRC Neuro-Polyvalent Snake Antivenin** for bites by cobras and kraits that cause paralysis
  - **TRC Hemato-Polyvalent Snake Antivenin** for bites by pit vipers that cause bleeding and tissue injury
- Both antivenoms are specific to species found in Cambodia and have low reaction rates

Who should receive antivenom?

- Antivenoms are not ‘magic cures’ for snake bite
  - There are limitations to what antivenoms can, and cannot achieve for the envenomed patient
  - Antivenoms can neutralise circulating snake venoms, but they do not cure tissue injury, restore depleted clotting factors, or repair damaged nerve terminals
- All patients with a positive 20WBCT, or clinical bleeding after suspected snake bite should receive appropriate antivenom in a therapeutic dosage
- All patients with systemic envenoming (including neurotoxicity, rhabdomyolysis, cardiovascular or renal abnormalities), or severe local envenoming need a therapeutic dose of appropriate antivenom

When should antivenom be given?

- Antivenom administration should never be delayed once it is indicated by early clinical evidence
- In patients bitten by kraits, the risk of irreversible neurotoxicity will be higher among patients who do not receive antivenom within the first 3-4 hours of the bite
- Always give an appropriate dose of the appropriate antivenom as soon as clinical evidence indicates that it is necessary
- It is never too late to give antivenom, but the best results occur when it is given early

Which antivenom should be given?

- If the patient has incoagulable blood (evidenced by a positive 20WBCT, clinical bleeding, or laboratory coagulation tests) or very severe local tissue injury, or a bite by a pit viper is suspected:
  - **TRC Hemato-Polyvalent Snake Antivenin** made by the Thai Red Cross Society is recommended

- If the patient has signs of neurotoxicity (minimally, ptosis, ophthalmoplegia or other cranial nerve palsy), or a bite by a cobra or krait is suspected:
  - **TRC Neuro-Polyvalent Snake Antivenin** made by the Thai Red Cross Society is recommended

How much should be given? (1)

- The dose of antivenom that is required depends to a large degree on the quantity of injected venom
- Every snake bite involves a different amount of injected venom
- Average venom yields from ‘milkings’ of venom often over-estimate the amount injected when a snake bites defensively
- Recommended starting doses of antivenom may not be sufficient to neutralise all circulating venom
- Some injected venom may also be retained at the bite site, entering the circulation hours or even days later, requiring administration of more antivenom

How much should be given? (2)

- A minimum starting dose of 2-3 vials of antivenom is recommended by the Thai Red Cross but these quantities are inadequate
- Depending on the severity of the envenomation, you may need to start with a higher dose:

Species	Antivenom	Starting Dose
Malayan pit viper	TRC Haemato Polyvalent	10 vials
Indo-Chinese Russell's viper	TRC Haemato Polyvalent	10 vials
Green pit vipers	TRC Haemato Polyvalent	2-5 vials
Monocellate cobra	TRC Neuro Polyvalent	10 vials
Indo-Chinese spitting cobra	TRC Neuro Polyvalent	10 vials
King cobra	TRC Neuro Polyvalent	20 vials
All species of Kraits	TRC Neuro Polyvalent	5 vials

How much should be given? (3)

- Rationing antivenom to a single vial per patient will result in ineffective treatment
- Large initial doses are needed because a single vial of antivenom does not contain enough antibodies to neutralise the amount of venom injected
- By giving an adequate dose, the costs of lengthy hospitalisation can be reduced, limbs can be saved, and risk of death from snake bite reduced
- Remember that these are starting doses: more antivenom may be needed if clinical improvement does not occur
- Review at least every 6 hours

How should antivenom be given?

- Lyophilised antivenoms must be reconstituted with 10 mL saline per vial
- Do not shake the vial to dissolve contents
- Swirl gently, or roll in the palms of the hands to prevent frothing of the solution
- Do not give test doses of antivenom
- Large doses of antivenom should be administered in an equal volume of normal saline, i.e.: 1 mL of intravenous fluid for each mL of antivenom
- Antivenom should be infused intravenously over no more than 30-60 minutes depending on the volume
- Always remain with the patient during infusion!

Adverse reactions to antivenom (1)

- The adverse reaction rate for some Indian-made antivenoms has been reported to be as high as 80%
- Half of these were severe anaphylactoid reactions
- The Thai Red Cross report a reaction rate for their products of 3.5%, but this is almost certainly an under-estimate
- Clinical studies indicate that premedication with drugs like adrenaline, antihistamine or steroids does not prevent adverse reactions to Indian antivenoms
- No data is currently available for current Thai Red Cross polyvalent antivenoms

Adverse reactions to antivenom (2)

- Monitor vitals signs (HR, BP, RR, T) during infusion of antivenom
- Have adequate quantities of adrenaline drawn up and ready in case an adverse reaction develops
- Watch for:
  - Urticarial eruptions, itching, complaints of ‘itchy throat’
  - Upper or lower airway restriction: wheeze or stridor
  - Dyspnoea
  - Blood pressure changes, especially hypotension, syncope
  - Arrhythmias (tachycardia or bradycardia)
  - Pyrexia, agitation, restlessness
- If these occur, stop the infusion and treat reaction

Adverse reactions to antivenom (3)

- Treatment of adverse reactions to antivenom:
  - Give intramuscular (i.m.) adrenaline as immediate treatment
  - Assess and if necessary protect airway and breathing *(wheezing is suggestive of lower airway obstruction, while stridor indicates upper airway occlusion)*
  - Give oxygen by face mask
  - Consider bronchodilators such as salbutamol (i.e.: asthma inhaler or nebuliser) or nebularised adrenaline for severe airway problems
  - Be prepared to intubate the airway if necessary
  - For hypotensive shock give suitable intravenous fluid replacement therapy

Adverse reactions to antivenom (4)

- Further steps for treatment of adverse reactions:
  - If there is a reaction H1 and H2 blockers and corticosteroid (hydrocortisone) may also need to be given, particularly if there is extensive, persistent urticarial rash
  - Be conscious of the fact that antihistamines may have sedative effects which can make subsequent neurological assessment difficult: they do however settle urticaria very quickly
  - Further adrenaline may be required for severe anaphylaxis, so be prepared to repeat the dose
  - Once the reaction has been treated, the antivenom infusion should be resumed under close supervision

Adrenaline doses for treating reactions

Paediatric Doses

Type:	Start with 1:1000 (1mg/ml) adrenaline	
Stock Dilution:	0.25 ml 1:1000 adrenaline diluted to volume of 2.5 ml	
Age group	Weight range (kg)	Dosage (ml)
1-3	Under 11	1.0
4-7	11-15	1.5
8-11	16-20	2.0

Adolescent & Adult Doses

Type:	Use 1:1000 (1mg/ml) adrenaline	
Body size	Weight range (kg)	Dosage (ml)
Small	21-50	0.25
Average	50-100	0.5
Large	> 100 kg	0.75

Serum sickness

- Some patients develop a delayed reaction that occurs between 5-10 days after antivenom has been administered.
- Symptoms include fever, rash/hives, arthralgia, lymphadenopathy and a flu-like illness.
- Advise the patient about serum sickness, and the usual symptoms and signs before discharge.
- The incidence and severity of serum sickness may be reduced by prescribing prednisone, at a dose of 50 mg (adult), or 1 mg/kg (child) for five days after the administration of the antivenom.

Summary

- Recognise the key indications for antivenom and if present do not delay administration
- Select the right antivenom for each situation based on the clinical presentation
- Give an appropriate therapeutic dose of antivenom, not just a single vial (which is insufficient)
- Monitor closely for reactions, and stop and treat them if they occur
- Restart antivenom when the patient is stable
- Assess the need for more antivenom every 6 hours
- Prescribe prednisone as prophylaxis against delayed serum sickness