For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

SNAKE ANTIVENIN (POLYVALENT) I.P.

स्नेक ॲन्टिवेनिन (पॉलिवॅलेन्ट) आय.पि.

Direction for use :

The Snake Antivenin is a preparation from the equine plasma of Hyperimmunised horses against Four common poisonous snakes of India. 1. Cobra (Najanaja) 2. Common Krait (Bungarus caeruleus), 3. Russells viper (Vipera russelli) and 4. Sawscaled viper (Echis carinatus). The preparation is a refined globulins, processed by enzyme digestion. Each ml. of the serum neutralizes the following quantities of standard venoms, Cobra - 0.6 mg, Common Krait - 0.45 mg. Russells viper - 0.6 mg and Sawscaled viper -0.45 mg. Preservative Phenol I.P. ≤ 0.25% w/v. The liquid preparation has to be stored between 2°C and 8° C. It should not be allowed to freeze.

Treatment of Snake Bite :

The management of Snake bite victims call for quick and positive action. The following First Aid measures are suggested.

1. First and foremost is to remove the patient to a well ventilated and quiet place infusing confidence in the patient and assuring that there is a major Psychological factor, efforts have to be made to combat the same.

2. Ligation :- Apply a ligature of some type above the bitten part to prevent the rapid absorption of venom. The ligature may be a handkerchief or a piece of cloth. A rubber ligature is by far the best. Ligature should not continue for over half an hour and must be released for a minute at intervals. Ligature should not be applied if an hour or more has elapsed after the bite.

3. Clean the bitten part with water without rubbing and dress it up with antiseptics taking care not to rub the part. Immobilize the bitten part as for a fracture.

Serum Treatment :

Only Polyvalent Snake Antivenin Serum can neutralize the venom in circulation. So the serum should be injected as soon as possible after the bite. As a first dose atleast 20 ml. of serum should be injected intravenously very slowly (not over 1.0 ml. per minute). The second dose should be repeated two hours after the first dose or even earlier if the symptoms persist. Further dose of the serum can be given depending on the condition of the patient. In case of viper bite, in addition to intravenous injection, some serum should be injected into and around the bitten area to prevent gangrene formation due to the destructive nature of the viper venom on tissue.

Symptoms :

Symptoms in the case of Elapine (Cobra and Krait) and Viperine (Russells Viper and Sawscaled Viper) are as follows:

As the reptile responsible for bites is seldom seen it will be possible to follow the general symptoms associated with Elapine or Viperine poisoning.

Cobra and Krait Poisoning :

In these cases general constitutional symptoms are observed than any local reaction like swelling. Owing to the predominance of neurotoxins there is creeping paralysis of muscles of eyelids, staggering gait, in co-ordination of speech, paralysis of limbs, dropping of head accompanied by nausea and vomiting. Death may ensure within a few minutes to several hours from respiratory failure caused by the neurotoxin. In Krait poisoning in addition there are convulsions and violent abdominal pain due to internal haemorrhages.

Russells viper and Saw Scaled Viper Poisoning :

No paralysis is observed in viperine poisoning. But a marked and severe local reaction at the site of bite is noticed and is characterized by persistent pain swelling with oozing of blood from the bite. This is followed by generalized vascular injury, widespread internal haemorrhage with tenderness and vomiting. Death is caused by intravascular clotting.

Serum Reactions :

Before treating the patient, it is necessary to enquire the following :-

1. Whether any Serum injection has been administered earlier.
2. Whether the patient has history of Asthma, Eczema or Drug Allergy.

A sensitivity test is carried out by injecting subcutaneously 0.1 ml. of serum in 1:10 dilution and observing for 30 minutes for any local or general reaction.

In allergic and sensitive patients, it is better to inject the Snake Antivenin Serum with antihistamines.

However the administration of serum in snake bite victims has to be decided taking into consideration the severity of patient condition and urgency of treatment must over-ride the danger of anaphylaxis. In such cases it may be better to inject 1.0 ml. of 1: 1000 Adrenaline intramuscularly at the same time to lessen the risk of anaphylaxis and half of the dose of Adrenaline may be repeated 15 minutes later should it be necessary.

Associated Treatment :

In viperine poisoning sedatives and analgesics relieve pain and nervousness. Use of corticosteroids minimises the serum reaction and allergic manifestations. Administration of Antibiotics is recommended to combat the local sepsis. Transfusion of a large amount of Normal Saline, better still Blood or Plasma is helpful in near collapsing patients. Sometimes tracheostomy and positive pressure ventilation (in case of respiratory paralysis) are other additional measures.

Storage :-

Liquid Snake Antivenin serum has to be stored between 2°C and 8°C., in a refrigerator. It should not be allowed to freeze.

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Manufactured in India by:
Biological E. Limited
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Wilderness and Environmental Medicine, **18,** 163–168 (2007)

EDITORIAL

Snake Antivenom Product Guidelines in India: "The Devil is in the Details"

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Venomous snakebite continues to exact a tremendous toll in human suffering and mortality in India. Contributing to this problem is the fact that all of the current Indian snake antivenom manufacturers include a great deal of misinformation in the package inserts and guidelines that accompany their products. Examples include erroneous recommendations regarding first aid, misleading information regarding the signs and symptoms to be anticipated after Indian snakebite, and misleading and ambiguous recommendations as to initial dosing and repeat dosing of antivenom. In addition, the significant problem of acute adverse reactions to Indian antivenoms is compounded by a lack of appropriate recommendations regarding prevention, diagnosis, and management of such reactions. It is the intent of this article to point out problems with the current Indian antivenom product guidelines and to encourage these manufacturers to produce new literature to accompany their products based on the best available evidence.

Key words: snake, antivenom, anaphylaxis, envenoming, first aid, AV dosage

Introduction

Bites by venomous snakes exact a great toll in terms of human morbidity and mortality in India. There are numerous factors that contribute to this suffering, and a great many ''easy'' solutions have been proposed as ways to reduce the impact of snakebites. For example, some have focused on the fact that agricultural workers in India tend not to wear footwear while in the fields.[1] Experience in some states, such as Rajasthan, however, has demonstrated that this is not a consistent factor leading to snakebites, because a large number of bites there occur to victims wearing footwear.[2] Others have cited a ''crisis'' in the supply of snake antivenom (AV), arguing that India has a shortage of AV and that this is a major factor.[3] However, the 6 main Indian AV manufacturers (Serum Institute of India,[4] VINS Bioproducts,[5] Bengal Chemicals and Pharmaceuticals,[6] Biological E,[7] Haffkine,[8] and Bharat Serums[9]) produce, between them, approximately 1 million vials of polyvalent AV annually. Assuming an average dose of 10 to 20 vials per envenomed victim, current capacity exists to treat 50 000 to 100 000 envenomed patients annually. If World Health Organization (WHO) estimates of 250 000 snake bites per annum in India are correct[10] and using the observation that approximately 20% of bites result in significant envenoming, then 50 000 envenomations requiring antiserum would be expected and AV supplies should be sufficient.[11–13] There are, of course, barriers to use of AV in individual cases of significant snakebite in India, such as reluctance on the part of some physicians to use the product due to unfamiliarity or fear of adverse drug reactions.

Another barrier to optimal management of venomous snakebite in India is the way in which physicians there are educated using, to a great degree, textbooks and other resources from western countries. Recommendations on snakebite management in these books are generally specifically aimed at American snakes and are not intended for use in India or other Asian or African countries.[14] Reliance on them as guidance in such matters as indications for initiating AV administration and dosing leads to errors in treating snakebite in India. For example, in the United States, AV (CroFab [Protherics Inc, London]) is recommended for administration to victims of snakebite with isolated progressive local findings.[15] Using such a strategy in India undoubtedly leads to pa-

No grants were received in connection with this paper.

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tients receiving unnecessary AV (see later) and waste of an important resource. What might be expected to be reliable sources of management information for Indian physicians, that is, the package inserts and product guides for all the AV products available to them, are, however, currently filled with erroneous and misleading information and recommendations. This misinformation includes recommendations on both first aid and definitive treatment and is pervasive in the literature from all 6 of the major manufacturers. It is our purpose in writing this paper to point out examples of this misinformation and to encourage the AV manufacturers to correct their product information.

First-aid advice

Four of the 6 manufacturers recommend a tight ligature as the principal first-aid method,[4,5,7,8] and 1 recommends an arterial tourniquet.[6] Those recommending a ligature suggest ''rubber ligatures are best.'' It is interesting that the wording is very close to that of Wall's recommendation in 1893[16]: ''There is only one way of doing this effectually. At once let a thick rubber band . . . be firmly bound on the limb above the bitten part.'' One of the striking aspects of the current product guidelines is that they seem to have remained untouched by modern developments and research and seem rooted in the first half of the 20th century. The use of tight ligatures and arterial tourniquets in the first-aid treatment of snakebite has been almost universally condemned by modern snakebite experts. The downsides of their use, of course, include risks of adding ischemic damage to the tissues[10]; increasing the necrotising effects of venoms[17,18]; and the potential adverse physiologic effects that may be seen on release, including hypotension, coagulopathy,[19] and neurotoxicity.[20] In addition, the lack of effectiveness of these measures in actually retarding venom flow has been well documented.[21–23]

One manufacturer[6] recommends deeply incising the bite site ''without, however, cutting any major arteries.'' They also recommend application of suction either mechanically or by mouth and the use of magnesium sulphate to eliminate ''tissue fluid containing the venom.'' The dangers of incision in victims of snakebites, especially in cases in which coagulopathy is present, are well known, as is the ineffectiveness of suction, including mechanical suction devices.[24] The potential for increasing envenomation by the use of a mechanical suction device by reducing the wound's natural oozing has also been reported.[25]

Anticipated symptoms

The guidelines on symptoms relating to each species are also misleading. Vipers specifically are identified as not giving rise to neurological symptoms,[4,5,7] even though the ability of the Russell's viper (*Daboia russelii*) to cause neurological deficits in both south India and Sri Lanka has been well described.[26,27] Bizarrely, one manufacturer,[4] suggests that the neurologic dysfunction caused by cobras and kraits presents as ''ascending paralysis'' beginning with the legs, when, in fact, neurotoxicity with these snakes occurs in descending fashion, commencing with muscles innervated by the cranial nerves.[17,28]

Antivenom recommendations

The initial dose of AV to be administered to a victim is widely recognized as a subject of debate. The majority of Indian AV manufacturers recommend a minimum of 2 vials as the initial starting dose.[4,6–8] One manufacturer makes no recommendation,[5] and another recommends a dosage scale depending on severity: 5 vials for local swelling, 5 to 10 vials for swelling beyond the bite and mild systemic symptoms, and 10 to 20 vials for systemic symptoms and coagulopathy,[9] recommendations remarkably similar to historically recommended starting doses for the US AV Antivenin [Crotalidae] Polyvalent [Wyeth-Ayerst Laboratories, Philadelphia, PA]).[29]

The starting dose takes on added significance in India given that doctors in peripheral hospitals often administer only this dose and then refer the patient to a better-equipped hospital at the district level. In one study, 90% of doctors in peripheral hospitals administered an inadequate dose of only approximately 2 vials.[30] This dose, therefore, frequently represents the total level of neutralization that victims will receive for the first several critical hours after bites while they are being sent to a higher level of care. It is during the initial minutes to hours after these bites that AV can be most effective in binding up free, circulating venom components, and getting an adequate starting dose on board is important. Two vials of any Indian polyvalent AV represent only 12 or 9 mg of total neutralizing capacity, depending on the target species. Each vial neutralizes a minimum of 6 mg of cobra (*Naja naja*) venom and Russell's viper (*D russelii*) venom and 4.5 mg of common krait (*Bungarus caeruleus*) venom and saw-scaled viper (*Echis carinatus*) venom.[4–9] Research indicates that Russell's vipers inject an average of 63 mg of venom in a bite.[31] Thus, 2 vials of AV as a starting dose would be expected to neutralize less than 20% of the venom load after such a bite! The initial dose should be more on the order of 10 vials. Even so-called ''low-dose'' strategies, in spite of their methodological weaknesses, recommend 6 vials as an initial starting dose.[32]

The use of AV in cases of purely local swelling is

inappropriate in India. A great many bites from nonvenomous or only mildly venomous species result in local tissue swelling, and, given the common inability of victims to correctly identify offending species, giving AV for local swelling results in a great many patients receiving AV unnecessarily.[33] The requirement for swelling to be severe, that is, involving at least half the bitten limb or rapidly crossing a joint, before beginning AV in India has been well established.[10]

Injecting AV around the site of the bite is recommended by 4 manufacturers.[4,6–8] The rationale is that local administration of AV prevents necrotic damage. However, there is no evidence that necrosis can be prevented by this practice.[34,35] In addition, local administration of AV can raise intracompartmental pressure and is painful, particularly in the digits, and should be avoided.[10,35,36]

Antivenom repeat dosing (timing)

Guidelines on repeat dosages of AV are also confusing and misleading. The recommendations vary considerably:

- Repeat after 1 or 2 hours if symptoms continue and every 6 hours until symptoms completely disappear.[5]
- Repeat after 2 hours or earlier if symptoms persist and every 6 hours until the symptoms completely disappear.[4,6]
- Repeat after 2 hours or earlier if the symptoms persist, then further dose ''depending on the condition of the patient.''[7]
- Repeat hourly until progressive local swelling ceases and systemic signs and symptoms ''disappear.''[9]
- Repeat after 1, 3, and/or 6 hours if clotting time is greater than 10 minutes and then infuse 2 more vials over 24 hours once coagulation is restored.[8]

In terms of their redosing recommendations, none of the guidelines makes a distinction between the 2 major forms of snake venom effects found in India, that is, neurotoxic or haemotoxic, and this distinction is critical to timing of repeat doses. It must be remembered that the objective of additional AV is to neutralize any circulating, unbound venom that was not neutralized by the initial dose. In the case of haemotoxic bites, the most effective approach is to repeat the dose of AV if coagulation is not restored after 6 hours.[37] The liver requires 6 hours to restore clotting factors,[10] and additional AV administration before this period has elapsed is potentially unnecessary and cannot be recommended based on any laboratory value that has not had sufficient time to improve. In the case of neurotoxic envenoming, however, an additional dose should be administered after 1 to 2 hours if the patient has not improved or if the condition has worsened. This period is appropriate because evidence has suggested that true reversibility of neurotoxic envenoming, that is, detaching tissue-bound postsynaptic venom neurotoxins, is only possible within the first 1 to 2 hours.[38] After that window of opportunity, the role of AV is to neutralize unbound venom. In the case of neurotoxic bites, therefore, only 2 doses of 10 vials need be administered within 2 to 3 hours, because this regimen both provides sufficient neutralizing capacity and facilitates any possible reversal of neurotoxicity.

Antivenom repeat dosing (indications)

Repeating AV administration on the basis of persistence of symptoms or progressive local swelling is a cause of considerable confusion. As stated, repeat dosing of AV is intended to neutralize venom that is still circulating and not neutralized by the starting dose. It is important to differentiate signs, symptoms, and investigations into those that show that the patient *is* currently envenomed (ie, indicating the continued presence of circulating, unbound and un-neutralized venom) vs those reflecting that the patient *was* envenomed but now has no circulating unbound venom requiring neutralization. Further AV is required in the former condition but *not* the latter. For example, a patient with high levels of blood urea nitrogen and serum creatinine is exhibiting signs of acute renal impairment. These findings are the result of prior venom effects that resulted in nephrotoxicity and are not indications, in themselves, that further AV is required. Similarly, whereas progressive local swelling that rapidly crosses a joint or involves at least half the bitten limb (in the absence of a tourniquet) is grounds for initially starting AV, such a finding on its own is unreliable in repeat dosing of AV. The most likely etiology of swelling after snakebite is the proteolytic enzymes, myotoxins, or hemorrhagic toxins causing local damage at or around the bite site. These include hyaluronidases, or ''spreading factors,'' designed to break down tissue to mediate venom dispersal. The release of fluids and breakdown products of tissues is the result of venom components that have bound to and affected their target cells, subsequently initiating inflammatory pathways. Progressive swelling merely reflects that such damage has been done and should not be used as the sole indication of remaining unbound, neutralizable venom.

The only reliable and readily available indications that a patient *is* currently envenomed are ongoing clinically significant bleeding, laboratory evidence of incoagulable blood (ie, the 20-minute whole blood clotting test performed 6 hours after an appropriate loading dose of AV), and worsening or persistent neurological signs if the

maximum of 20 vials has not been given. These are the key criteria for repeating doses of AV in India.

Lack of clarity as to which criteria signal the need for repeat AV dosing causes very large and unnecessary doses to be given.[39] This is particularly the case in swelling, which may persist or increase for days after circulating venom has been neutralized. Similarly, neurotoxic victims have been given massive doses of AV because the requirement for ventilatory support was seen as a circumstance that required reversal before AV is stopped.

The advice to administer a further 2 vials of Indian AV, once coagulation has been restored,[8] is completely unnecessary. Although the concept of recurrent envenomation is acknowledged,[10] this usually occurs when an AV with a short half-life (eg, Fab AV) is used. Indian AVs contain $F(ab)_2$ antibody fragments and have a half-life of approximately 90 hours.[10] Thus, recurrence is uncommon in India, and routine use of prophylactic AV is not justified by the evidence, is a waste of resources, and adds additional financial costs and risks of adverse drug reactions.

Antivenom reactions

Indian AV has a well-documented record for frequently causing adverse reactions that are either anaphylactoid or pyrogenic.[40,41] These reactions occur in 60 to 80% of patients receiving AV.[41] Current guidelines from the product manufacturers are sorely lacking in terms of assisting physicians in preparing for and managing these acute reactions.

Five of 6 of the major Indian AV manufacturers recommend skin sensitivity testing as a means of predicting adverse AV reactions.[4,5,7–9] The usefulness of skin testing has been in doubt for more than a quarter of a century.[42] Although it was hoped that such testing could detect patients at risk for immunoglobulin E–mediated sensitivity reactions to AV, the majority of these acute reactions are nonimmunoglobulin E mediated (ie, anaphylactoid), and such testing is, therefore, of no benefit.[10,43] In addition, skin testing carries the risk of inducing an acute reaction in and of itself,[36] and delays the initiation of AV administration for at least the 30 minutes that has been recommended as the time needed to interpret the results. Skin testing should no longer be recommended by AV manufacturers.

One manufacturer recommends keeping patients under observation for anaphylactoid reactions for 30 minutes after administration of AV.[4,8] This period is far too short. The required observation period is at least 1 hour, and the observation should be active and include checking under clothing for hidden urticaria, because there is evidence that many anaphylactoid reactions are missed.[44]

Supportive measures

The most alarming of the supportive measures recommended by 3 of the Indian AV manufacturers is the use of strychnine for the treatment of hypotension.[4,6,8] The 1911 edition of the *Encyclopaedia Britannica* had the following entry relating to the treatment of shock: ''treatment, which comprise external stimulation over the heart by mustard poultices or turpentine stupes . . . These different measures may be supplemented by the administration of stimulants by the mouth, or, if the patient cannot swallow, by subcutaneous injection of brandy, ether or a solution of strychnine.'' The use of strychnine in the treatment of shock was recommended until the mid 20th century, especially in military medical guides.[45] Its use came into question, however, in 1929.[46] Interestingly, the 3 Indian AV manufacturers that recommend the use of strychnine are the government manufacturers who have existed since around the mid 20th century.

Current recommendations for the treatment of hypotension in snakebite depend on the cause. The most common cause is hypovolaemia (due to venous pooling of blood and third spacing of fluids). Primary management in this case involves adequate fluid resuscitation with crystalloids and, if needed and available, albumin. Once the intravascular volume has been restored, vasopressor agents may be added.[10,35] Blood products may occasionally be required in victims suffering from haemorrhagic shock but only after adequate AV has been given. Hypotension may also occur in the face of an anaphylactoid reaction to AV. In this situation, the reaction should be managed with appropriate doses of epinephrine (adrenaline) and such secondary measures as antihistamines and steroids. The use of strychnine has no place in modern snakebite treatment.

Also ill-advised is the use of aspirin in viper bites, as recommended by one manufacturer.[4] Aspirin's inhibitory effect on thromboxane A_2 and prevention of platelet aggregation may complicate venom-induced coagulopathy. Pain killers, such as paracetamol, with or without narcotics should be employed instead.

Conclusions

The current AV guidelines produced by Indian manufacturers are clearly inadequate and dangerous and seem to be based on historical recommendations long since superseded by medical research. It is incumbent on pharmaceutical manufacturers to ensure that their products,

including the accompanying instructional inserts, are as safe and effective as possible. As India seeks to dramatically improve its approach to snakebite management, it is essential that the AV manufacturers become active participants in that effort. They can do this, not just by producing better quality AVs and introducing new antiserums, but by providing doctors with guidelines and instructions that reflect current benchmark practices.

These recommendations should include:

- Accurate description of anticipated signs and symptoms.
- Sound advice on first-aid measures based on what current evidence exists.
- Abandoning recommendations for skin tests.
- Uniform recommendations for ''indications'' for initiating AV.
- Precise starting dose recommendations.
- More specific guidelines for redosing schedules.
- Accurate description of precautions related to adverse drug reactions, including recognition and management.

At the Indian National Snakebite Protocol Consultation Meeting (August 2, 2007, Delhi) a recommendation was made that all Indian AV manufacturers change their product inserts to reflect the newly ratified National Snakebite Protocol. This was supported by Haffkine Bio-Pharmaceutical Corporation Ltd, and it is our hope that all manufacturers will now follow suit.

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