Protocol for administration of Anti Snake Venom

Poly anti snake venom is effective for venoms big four snakes in India. The big four snakes include Common cobra, Common krait, Russell viper and Saw scaled viper. There is no specific anti snake venom available for different types of snake. Snake antivenoms are produced by using the serum of animals immunized with venom, and are a specific treatment for snake envenomation. Antivenom is given to reverse systemic symptoms and minimize and control further local injury. In general, antivenoms are effective and are able to reduce morbidity and mortality. However, the benefits of antivenom use are dependent on proper dosing and timely administration.

Adverse drug reaction to Anti snake venom

The two primary risks associated with antivenom therapy are acute anaphylaxis or anaphylactoid reactions (mild to severe) and serum sickness. Symptoms can begin as a cough, tachycardia, itching (especially of the scalp), urticaria, fever, nausea, vomiting and headache. Systemic reactions can progress to include: hypotension, bronchospasm and angioedema. Severe anaphylactic shock is a rare complication of antivenom therapy, but may be fatal.

Pharmacologic Mechanism

Antivenoms are effective based on their ability to complex an antigen with the appropriate antibody. The antigen is neutralized (Chippaux & Goyffon, 1998).

Therapeutic Dose

Adult

A) General

The dose of antivenom used is dependent on the snake, the time between the bite and antivenom therapy, clinical symptoms (e.g., neurotoxicity, coagulopathies, cardiototoxicity, progressive rapid swelling, or bites on fingers or toes). The precise amount of antivenom is often unknown, but high doses may be necessary to effectively treat symptoms. Clinical response is generally used to guide dosing.
The intravenous route is recommended because of rapid distribution and the bioavailability of the antivenom are higher than other routes. It is usually diluted in 0.9% saline and given by slow intravenous infusion. This method allows for easy control of adverse events. Intramuscular injection is considered less efficient, but does tend to minimize severe adverse effects. Avoid subcutaneous injections at the site of the bite, because it is ineffective, painful and may increase local complications (Chippaux&Goyffon, 1998).

**Pediatric**

**A) General**

1) Generally, antivenom dosing for children should be the same as an adult dose (Warrell, 1995). Refer to manufacture's information as indicated.

**Dose**

There is no universal agreement on exact dose of antivenom. Antivenom is administered at a dose of 5 ml/min or diluted in Isotonic fluid and infused over 30-60 min. dress venipuncture sites with a pressure bandage. Injection of anti venom into the fang marks is probably ineffective and painful.

Epinephrine (adrenaline) should always be drawn up in readiness before antivenom is administered. Antivenom should be given by the intravenous route whenever possible.

**Anti venom Administration Guidelines**

**Test dose** of 0.02-0.03 ml of 1:10 diluted antivenom in normal saline must be given intradermally. Test is deemed to be positive if an urticarial wheal with erythema develops at test site within 30 min. In such a case, antivenom must be given only as a life-saving or limb-saving measure after desensitization.

**Desensitization**

Begin with Subcutaneous administration of 0.1 ml of 1:100 diluted antivenom and increase dose every 15 min as follows:0.2 ml and 0.5 ml. Repeat the regimen with 1:10 and 1 and finally with
undiluted antivenom. At any point of time, hypersensitivity reaction occur, administer adrenaline immediately.

Two methods of administration are recommended:

(1) Intravenous “push” injection: reconstituted freeze-dried antivenom or neat liquid antivenom is given by slow intravenous injection (not more than 2 ml/minute). This method has the advantage that the doctor/nurse/dispenser giving the antivenom must remain with the patient during the time when some early reactions may develop. It is also economical, saving the use of intravenous fluids, giving sets, cannulae etc.

(2) Intravenous infusion: reconstituted freeze-dried or neat liquid antivenom is diluted in approximately 5-10 ml of isotonic fluid per kg body weight (ie 250-500 ml of isotonic saline or 5% dextrose in the case of an adult patient) and is infused at a constant rate over a period of about one hour.

Note: Local administration of antivenom at the site of the bite is not recommended. Although this route may seem rational, it should not be used as it is extremely painful, may increase intracompartmental pressure and has not been shown to be effective.

**Intramuscular injection of antivenom**

Antivenoms are large molecules (F(ab)2 fragments or sometimes whole IgG) which, after intramuscular injection, are absorbed slowly via lymphatics. Bioavailability is poor, especially after intragluteal injection and blood levels of antivenom never reach those achieved rapidly by intravenous administration. Other disadvantages are the pain of injection of large volumes of antivenom and the risk of haematoma formation in patients with haemostatic abnormalities.

Epinephrine (adrenaline) is given intramuscularly (into the deltoid muscle or the upper lateral thigh) in an initial dose of 0.5 mg for adults, 0.01 mg/kg body weight for children. Severe, life-threatening anaphylaxis can evolve very rapidly and so epinephrine (adrenaline) should be given at the very first sign of a reaction, even when only a few spots of urticaria have appeared or at the start of itching, tachycardia or restlessness. The dose can be repeated every 5-10 minutes if the patient’s condition is deteriorating.
At the earliest sign of a reaction:

- Antivenom administration must be temporarily suspended
- Epinephrine (adrenaline) (0.1% solution, 1 in 1,000, 1 mg/ml) is the effective treatment for early anaphylactic and pyrogenic antivenom reactions

**Additional treatment:** After epinephrine (adrenaline), an anti H1 antihistamine such as chlorpheniramine maleate (adults 10 mg, children 0.2 mg/kg by intravenous injection over a few minutes) should be given followed by intravenous hydrocortisone (adults 100 mg, children 2 mg/kg body weight). The corticosteroid is unlikely to act for several hours, but may prevent recurrent anaphylaxis.

There is increasing evidence that anti H2 antihistamines such as cimetidine or ranitidine have a role in the treatment of severe anaphylaxis. Both drugs are given, diluted in 20 ml isotonic saline, by slow intravenous injection (over 2 minutes).

Doses: cimetidine – adults 200 mg, children 4 mg/kg;

Ranitidine – adults 50 mg, children 1 mg/kg.

Treatment of late (serum sickness) reactions

Late (serum sickness) reactions usually respond to a 5-day course of oral antihistamine. Patients who fail to respond in 24-48 hours should be given a 5-day course of prednisolone.

Doses: Chlorpheniramine: adults 2 mg six hourly, children 0.25 mg/kg /day in divided doses

Prednisolone: adults 5 mg six hourly, children 0.7 mg/kg/day in divided doses for 5-7 days

**Observation of the response to antivenom**

If an adequate dose of appropriate antivenom has been administered, the following responses may be seen.

- General: the patient feels better. Nausea, headache and generalised aches and pains may disappear very quickly. This may be partly attributable to a placebo effect.
• Spontaneous systemic bleeding (eg from the gums) usually stops within 15-30 minutes.

• Blood coagulability (as measured by 20WBCT) is usually restored in 3-9 hours. Bleeding from new and partly healed wounds usually stops much sooner than this.

• In shocked patients, blood pressure may increase within the first 30-60 minutes and arrhythmias such as sinus bradycardia may resolve.

• Neurotoxic envenoming of the post-synaptic type (cobra bites) may begin to improve as early as 30 minutes after antivenom, but usually take several hours. Envenoming with presynaptic toxins (kraits and sea snakes) is unlikely to respond in this way.

Criteria for giving more antivenom

• Persistence or recurrence of blood incoagulability after 6 hr of bleeding after 1-2 hr

• Deteriorating neurotoxic or cardiovascular signs after 1-2 hr

If the blood remains incoagulable (as measured by 20WBCT) six hours after the initial dose of antivenom, the same dose should be repeated. This is based on the observation that, if a large dose of antivenom (more than enough to neutralise the venom procoagulant enzymes) is given initially, the time taken for the liver to restore coagulable levels of fibrinogen and other clotting factors is 3-9 hours. In patients who continue to bleed briskly, the dose of antivenom should be repeated within 1-2 hours. In case of deteriorating neurotoxicity or cardiovascular signs, the initial dose of antivenom should be repeated after 1-2 hours, and full supportive treatment must be considered.

Maximum Tolerated Exposure

A) General/Summary

1) Severe anaphylactic shock is a rare complication of antivenom therapy and occurs in less than one in a thousand treatments (Chippaux&Goyffon, 1998).

2) The two primary risks associated with antivenom therapy are anaphylaxis and serum sickness (Warrell, 1995; Chippaux&Goyffon, 1998).
Treatment Overview

Parenteral Exposure

A) Summary - Antivenom therapy is the primary treatment of snake envenomation. Antivenom is indicated as soon as possible following a significant envenomation, but may be given many hours after exposure.

B) Hypersensitivity Reaction - Because hypersensitivity reactions are possible, the patient should be closely monitored. Airway swelling or bronchospasm requires immediate cessation of antivenom and aggressive treatment. Basic life support measures and close monitoring in an intensive care setting are recommended.

1) Allergic Reaction: Mild/Moderate: antihistamines with or without inhaled beta agonists, corticosteroids or epinephrine. SEVERE: oxygen, aggressive airway management, antihistamines, epinephrine (ADULT: 0.3 to 0.5 mL of a 1:1000 solution subcutaneously; CHILD: 0.01 mL/kg, 0.5 ml max; may repeat in 20 to 30 min), corticosteroids, ECG monitoring, and IV fluids.

2) Hypersensitivity Testing - While patients with positive skin tests to intradermal injection of antivenom are more likely to develop severe acute allergic reactions to antivenom, a negative skin test does not reliably exclude the development of an acute allergic reaction. Many manufacturers no longer recommend the use of skin testing prior to antivenom administration; however some clinicians still advocate their use with certain antivenoms.

C) Premedication - Pretreatment, with epinephrine, antihistamines, and/or corticosteroids, has been widely practiced in some areas of the world, but it remains controversial.

D) Hypotension: Infuse 10 to 20 ml/kg isotonic fluid. If hypotension persists, administer dopamine (5 to 20 mcg/kg/min) or norepinephrine (ADULT: begin infusion at 0.5 to 1 mcg/min; CHILD: begin infusion at 0.1 mcg/kg/min); titrate to desired response.

Laboratory/Monitoring Parameters

A) No specific lab work (CBC, electrolytes, urinalysis) is needed unless otherwise clinically indicated.
Kinetics

Distribution

A) Volume Of Distribution

1) The composition of antivenom can vary depending on the degree of purification and the degree of antibody fragments [IgG, Fa(ab')2 or F(ab)]. In general, venom distributes mainly into the tissue compartments, while IgG and F(ab')2 distribute only weakly out of the plasma volume; therefore they are unable to neutralize antigens within the tissue (Chippaux&Goyffon, 1998).

2) F(ab')2 fragments - volume of distribution is approximately twice as high as plasma volume, which suggests a poor distribution in tissue. The fragments however distribute more rapidly than whole IgG (Chippaux&Goyffon, 1998).

B) Peak Plasma Level

1) IgG - the concentration peak is reached in 6 hours in superficial tissue and 30 hours for deep tissue (Chippaux&Goyffon, 1998).

2) F(ab')2 fragments reach a concentration peak in 1 hour in superficial tissue and 6 hours in deep tissue (Chippaux&Goyffon, 1998).

Excretion

1. Kidney

A) F(ab) is excreted via the kidneys. This is only possible when F(ab) is free or combined with a hapten and not when its combined with venom proteins. A potential risk of renal lesions due to F(ab) immune complexes have been observed in some patients, as noted by a significant decrease in the rate of creatinine clearance (Chippaux&Goyffon, 1998).

2. Other

1) IgG and F(ab')2 are excreted via cells of the immune system. Glomerular filtration stops for molecules that are higher than 50 to 60 kDa (Chippaux&Goyffon, 1998).
Complications

The two primary risks associated with antivenom therapy are anaphylaxis and serum sickness.

Contraindications

There is no absolute contraindication to antivenom treatment, but patients who have reacted to horse (equine) or sheep (ovine) serum in the past (for example after treatment with equine anti-tetanus serum, equine anti-rabies serum or equine or ovine antivenom) and those with a strong history of atopic diseases (especially severe asthma) should be given antivenom only if they have signs of systemic envenoming. Prophylaxis in high risk patients, in the absence of any prophylactic regimen that has proved effective in clinical trials, these high risk patients may be pre-treated empirically with subcutaneous epinephrine (adrenaline), intravenous antihistamines (both anti-H1, such as promethazine or chloramphenicol; and anti- H2, such as cimetidine or ranitidine) and corticosteroid. In asthmatic patients, prophylactic use of an inhaled adrenergic agonist such as salbutamol may prevent bronchospasm.