DRUG ALERT

Regional Pharmacovigilance Centre (South)

Department of Pharmacology, JIPMER, Pondicherry-605 006, India

Co-ordinator: Dr. C. Adithan E-mail: adr@jipmer.edu

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ANTI SNAKE VENOM (ASV) REACTIONS – A PERSPECTIVE

ASV usage remains a very risky business. Incidence of early adverse reactions varies between 5-80%. In my experience it is 60%. Many other issues receive much attention, but ASV reactions in India have been accepted at its current level. The deaths due to ASV reactions are wrongly attributed to envenomation. Moreover reports from pharmacovigilance centres do not mention whether any prophylaxis is used to prevent reactions. These would tend to understate the current level (Table 1).

ASV is the immunoglobulin (usually the enzyme refined $F(ab)_2$ fragment of IgG) purified from serum or plasma of horse or sheep that has been immunised with the venoms of one or more species of snake. Polyvalent or polyspecific antivenom neutralises the venoms of several different species of snakes, usually the most important species in a particular geographical area. ASV treatment is recommended if and when a patient with proven or suspected snake bite develops one or more signs of systemic envenomation – hemo or neurotoxicity.

The initial dose of ASV is empirical. In the absence of any objective method of establishing species and level of envenomation, doctors have to rely on symptomatology to estimate the level of envenomation, even though this is known to be highly unreliable. There is only a clinical perspective scale to classify snakebite victims as mild, moderate and severe envenomation and the dose of ASV being arbitrarily fixed at 50 ml (5 vials), 100 ml (10 vials), and 150 ml (15 vials) respectively. Snakes inject the same dose of venom into children and adults. Children are therefore given exactly the same dose of antivenom as adults.

In hemotoxic bites, adult medical clinics have standardized the following protocol: For mild envenomation – 30 ml (bolus) stat and for moderate and severe envenomation – 70 ml (bolus) stat, then 30ml 6 hourly continuous infusion till clotting time normalizes. Neurotoxic snake bites are clinically considered as severe envenomation.

Criteria for giving more antivenom: (1) Persistence or recurrence of blood incoagulability after 6 hrs of bleeding. (2) Deteriorating neurotoxic or cardiovascular signs after 1-2 hrs.

Table 1. ADRs to ASV reported from RPC (South) JIPMER, Pondicherry, during April to November, 2005.

Pharmacovigilance centre	No. of ADRs
JIPMER, Pondicherry	20
Sri Devaraj Urs Medical College, Kolar	3
Manipal College of Pharmaceutical Sciences, Manipal	4
Annamalai University, Chidambaram	2
JSS Medical College and Hospital, Mysore	2
JSS College of Pharmacy, Ootacamund	1
Total	**32**

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 1 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, iv 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 (i.e., 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. Both are used widely and found effective. There is not much difference between low dose continuous and bolus regimens in our experience.

Antivenom reactions:

Type I- Early anaphylactic reactions (within 5-180 min of starting antivenom): It may manifest as itching, urticaria, dry cough, abdominal colic, fever, nausea, tachycardia, hypotension, bronchospasm, and angioedema. Few may develop life threatening anaphylactic shock. In most cases, these reactions are not truly "allergic". They are not IgE-mediated type I hypersensitivity reactions to horse or sheep proteins. Complement activation by IgG aggregates or residual Fc fragments or direct stimulation of mast cells or basophils by the proteins in ASV are likely mechanisms for these reactions.

Type II Pyrogenic reactions (within 1-2 hours of treatment): The patient may have rigors, fever, vasodilatation, fall in BP. These reactions are caused by pyrogen contamination during the manufacturing process.

Late (Serum sickness type) reactions (within 1-12 days after treatment): The clinical features include fever, nausea, vomiting, diarrhea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swellings, mononeuritis multiplex, proteinuria with immune complex nephritis and rarely encephalopathy. This reaction is less likely to develop in patients who had early reactions and are treated with antihistamines and corticosteroids.

Treatment of early anaphylactic and pyrogenic ASV reactions:

ASV administration is temporarily stopped at the earliest sign of a reaction. Adrenaline (0.1% solution) 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 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.

In addition to adrenaline, H_1 antagonist such as chlorpheniramine maleate (adults - 10 mg, children - 0.2 mg/kg) is given intravenously over a few minutes followed by intravenous hydrocortisone (adults - 100 mg, children - 2 mg/kg body weight). The corticosteroid is unlikely to act immediately, but may prevent recurrent anaphylaxis.

Further H_2 antagonists such as cimetidine (adults - 200 mg, children - 4 mg/kg) or ranitidine (adults - 50 mg, children - 1 mg/kg) diluted in 20 ml of isotonic saline, is given by slow i.v. injection over 2 minutes.

In pyrogenic reactions the patient must also be cooled physically and with antipyretics (e.g. paracetamol p.o. or suppository). Intravenous fluids should be given to correct hypovolemia.

Treatment of late (serum sickness) reactions

Late (serum sickness) reactions usually respond to a 5-day course of oral antihistamine (chlorpheniramine maleate: adults - 2 mg sixth hourly, children - 0.25 mg/kg /day in divided doses). Patients who fail to respond with in 24-48 hours should be given a 5-day course of prednisolone (adults - 5 mg sixth hourly, children - 0.7 mg/kg/day in divided doses for 5-7 days)

Research issues

When an ASV reaction is encountered, it is often commented that lyophilized antivenom would have been better compared to liquid preparation. The notion that liquid preparations may have more proteins and impurity which result in higher rate of reactions is not correct. Lyophilisation is merely freeze-drying of refined horse proteins to prolong its shelf life in hot climates. Its composition is exactly the same as liquid antiserum, but incorrect freeze-drying may denature the proteins, making the powder difficult to redissolve and increasing the rate of reactions.

Some investigators believe that ASV reactions are seen more in hemotoxic bites than neurotoxic ones. A clinical trial to establish whether neuro or hemotoxic bites cause different levels of reactions will be very difficult due to existing variation in the batch quality of ASV. Two randomized double blind control studies are underway in India to determine if prophylactic adrenaline or steroids reduce the problem. Standard practice guidelines for tackling ASV reactions must be evolved and followed at every healthcare facility.

Quantifying the amount and nature of venom in the victim will render objectivity to ASV therapy. Development of assays for detection and quantification of venom in the victim should be our research focus in in order to reduce snakebite mortality.

Present status

ASV reactions are more linked to the manufacturer of ASV than the nature of venom. The manufacturing process has a considerable role to play. ASV available for use has escaped the net of mandatory stringent clinical trials. The manufacturers have to ensure high standards of quality control during ASV production.

Key points

- ASV is the only specific antidote to snake venom in India
- Children must be given the same dose of ASV as adults
- Observe the patient for at least 1 hour after starting ASV for early detection of reactions
- Adrenaline should always be drawn up in readiness before ASV is administered. It should be given at the very first sign of a reaction
- Skin and conjunctival "hypersensitivity" tests do not predict the large majority of early (anaphylactic) or late (serum sickness type) ASV reactions
- For fear of reactions ASV should not be withheld for a snake bite victim when indicated
- Local administration of ASV at the site of the bite is not recommended
- Close monitoring, desensitization and supportive care are crucial to management

Prof. S. Mahadevan,
Dept. of Pediatrics, JIPMER, Pondicherry
E-mail:smaha1232@rediffmail.com