Adverse reactions to snake antivenom, and their prevention and treatment

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bcp.12739

Conflicts of interest: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Introduction

Snakebite is a WHO-listed Neglected Tropical Disease. Bites result in an estimated 421,000 envenomings and 20,000 deaths globally each year, although the incidence may be as high as 1,800,000 envenomings and 94,000 deaths [1]. Envenoming also causes considerable physical and psychological disability among survivors [2, 3]. The highest snakebite burden is in rural areas of South Asia, Southeast Asia, and sub-Saharan Africa, which experience high morbidity and mortality. This is because of poor access to, often suboptimal, health services and a scarcity of safe and effective antivenom which is the mainstay of treatment of snakebite envenoming [4, 5].

Adverse reactions to available snake antivenoms are common in many parts of the world where snakebite is prevalent; both acute (anaphylactic or pyrogenic) and delayed (serum sickness type) reactions occur [5].

Acute reactions

Acute reactions to antivenom cause the greatest problem, and clinicians have to deal with them as much as managing envenoming. In most cases symptoms are mild (urticaria, nausea, vomiting, headache, and fever), but severe systemic anaphylaxis, including hypotension, cyanosis, and altered level of consciousness may develop in up to 40% of cases [6, 7, 8, 9]. In Sri Lanka, where only Indian manufactured polyvalent antivenoms are available, reported severe reaction rates may be as high as 43% [10, 11, 12, 13]. Therefore, increasing the safety of antivenoms used in the treatment of snakebite victims is a priority.

The mechanism of acute reactions to antivenom is uncertain. Acute reactions may be due to type I hypersensitivity, but antivenom reactions often occur in those with no previous

exposure to equine proteins. Although some commercially available antivenoms are anti-complementary in vitro, complement activation has not been clearly demonstrated in patients with antivenom reactions [6, 14, 15]. Early reactions are most likely to be due to a combination of type I hypersensitivity, complement activation, and the effect of aggregates of immunoglobulin or immunoglobulin fragments, including Fc, which can be found in even highly purified antivenoms [16]. Although there are theoretical reasons why cleaving of the IgG molecule into smaller fragments should reduce the incidence of antivenom reactions, this has not been demonstrated in clinical studies, and reaction rates appear to also depend as much on the manufacturing process [17,18,19]. Stone et al [20] studied the immune response to snake envenoming and Indian manufactured antivenoms by measuring plasma concentrations of cytokines, anaphylatoxins (C3a, C4a, C5a which are markers of complement activation), mast cell tryptase, and histamine in 120 Sri Lankan snakebite victims. Their results suggest that antivenom reactions were not complement mediated and were possibly due to IgG immunoglobulin complexes and impurities in the antivenom.

Although improving the quality of antivenom is the solution, several different methods have been attempted to reduce the current high rates of reactions to many of the available antivenoms. Administering a small test dose of antivenom to identify patients who may develop acute adverse reactions to the antivenom is not sufficiently sensitive or specific and can itself cause anaphylactic reactions [6]. Slow intravenous infusion of antivenom instead of a bolus injection has been proposed as a way of reducing reaction rates, although comparative studies of methods of administration found no difference in the rates of severe systemic reactions between a 30-minute infusion and intravenous injection over 10 minutes [21]. Moreover, there is also no evidence that monovalent antivenoms result in significantly fewer adverse effects than polyvalent antivenoms [22]. Given the failure of these interventions to

predict or reduce acute reactions, it is not surprising that pharmacological prophylaxis has been used to reduce acute adverse reactions to antivenom.

Premedication for antivenom treatment

Although the theoretical basis for their use is unclear and there is no clear evidence of benefit, empirical prophylactic use of hydrocortisone and antihistamines before infusion of antivenom is practised widely (12). Antihistamines counter only the effects of released histamine and do not prevent further release. One small, randomized controlled trial demonstrated no benefit from the routine use of antihistamines [23]. Hydrocortisone, by virtue of its mechanism of action takes time to act. It is unlikely to be effective as a prophylactic against acute adverse reactions that can develop almost immediately after antivenom treatment, which is very often administered urgently to snakebite victims. A small study published in 2004 suggests that intravenous hydrocortisone alone is ineffective in preventing acute adverse reactions to antivenom, but if given together with intravenous chlorpheniramine (an antihistamine) adverse effects of antivenom may be reduced [12]. However, this trial recruited only 52 patients, almost all observed reactions to antivenom were mild or moderate (2 were severe), and the study was not powered to investigate the efficacy of chlorpheniramine alone. This makes clear interpretation of the study results and recommendations on the usefulness of pretreatment with steroids and antihistamines to prevent acute reactions to antivenom difficult.

Although there were a few early reports of its use in Australia [24], there is a general reluctance to use adrenaline because of potential adverse effects. In one study involving 105 patients, low-dose adrenaline given subcutaneously, immediately before administration of antivenom to snakebite victims significantly reduced the incidence of acute adverse reactions

[10]. Unfortunately, as a result of this significant benefit, the independent Data Monitoring Committee (DMC) of this study stopped the trial early. This precluded the investigators from establishing the safety of low-dose adrenaline in a prophylactic role [25], especially in relation to the risk of intra-cerebral haemorrhage [26, 27]. Another study, which examined antivenom use, premedication, early adverse reactions and patient outcomes after snake bite retrospectively in rural Papua New Guinea found that adrenaline premedication appeared to significantly reduce acute adverse reaction rates to antivenom (7.7%), compared to patients pre-medicated with promethazine and / or hydrocortisone (28.3%) or with patients not receiving any premedication (28%) [28]. This study has subsequently been criticised for its retrospective design, lack of standardised definitions, and a selective statistical analysis that did not correct for multiple comparisons.

In view of the uncertainty about the safety and efficacy of pre-treatment to reduce or prevent adverse reactions to antivenom, de Silva *et al* conducted a randomized, placebo-controlled, double-blind trial to determine whether low-dose adrenaline, promethazine, and hydrocortisone, alone and in all possible combinations, are significantly better than placebo in preventing acute adverse reactions to antivenom in snakebite victims [13]. This large factorial design study randomized more than 1000 eligible patients over four years. The study reported an acute reaction rate of 75% to the antivenom; 43% of them were severe reactions. A severe reaction was defined by the investigators as a systolic blood pressure less than 80 mmHg, altered level of consciousness or cyanosis. Almost 90% of reactions observed during the study occurred within the first hour after administration of antivenom, underscoring the acute nature of these reactions. The investigators found that administration of adrenaline significantly and substantially reduced the risk of severe adverse reactions compared with placebo in the first hour (43% reduction) and that this effect was still apparent at 48 h (38%

reduction). However, neither hydrocortisone nor promethazine had any clear effect on reducing the risk of acute reactions. This study also unequivocally demonstrated that a small dose of subcutaneous adrenaline (250 µg) is safe after snakebite, even where there is coagulopathy. While pre-treatment with hydrocortisone or promethazine did not significantly reduce severe reaction rates to antivenom, hydrocortisone negated the beneficial effects of adrenaline when these treatments were given together [13]. Given that hydrocortisone and promethazine have no benefit their current widespread empirical use as a pre-treatment before antivenom administration should be discouraged. At present, only adrenaline has been shown to be safe and effective in the prevention of acute reactions to antivenom with any evidence base.

Treatment of early reactions / anaphylaxis

The treatment of anaphylactic reactions to antivenom involves pharmacologic and non-pharmacologic interventions (Table 1). Non-pharmacologic measures include temporarily stopping the antivenom infusion, airway management and fluid resuscitation. The mainstay of pharmacologic management is adrenaline given intramuscularly, which pharmacokinetic studies have shown to be superior to subcutaneous administration. Antihistamines and corticosteroids are no longer recommended for the treatment of anaphylaxis [29, 30]. Patients who do not respond to intramuscular adrenaline and fluid resuscitation may require intravenous infusions of adrenaline. When the reactions are controlled and the patient is haemodynamically stable the antivenom infusion is started again, initially at a slower rate. This may result in a recurrence of acute reactions, which might necessitate repeat administration of adrenaline. This is a challenge that clinicians managing snake envenomation have to face regularly in countries where snakebite is prevalent. [See references 31 and 32 for a detailed description of anaphylaxis and its management].

Pyrogenic Reactions

Pyrogenic reactions to antivenom are caused by pyrogen contamination during manufacture and may include chills, rigors, fever, myalgia, headache, tachycardia and hypotension secondary to vasodilataion [33]. In children, febrile convulsions may be precipitated. Bacterial lipopolysaccharides are the most common pyrogens in antivenoms. Reactions typically occur within the first hour of starting an antivenom infusion. Treatment includes reducing fever by cooling physically and anti-pyretics (paracetamol). Intravenous fluids and adrenaline may be required in severe cases with hypotension. Prevention of these reactions is by adherence to good manufacturing practices to avoid contamination of antivenom with microbial products.

Serum sickness (delayed antivenom reaction)

Although the incidence and characteristics of serum sickness following the administration of antivenoms is poorly defined (mostly because patients rarely return to health centres after discharge or are not adequately followed up once at home), the information available shows that it can vary considerably across geographical locations and snake antivenom type. Serum sickness was first described in 1905 by Clemens von Pirquet and Bela Schick who provided a pathogenic description and characterization of serum sickness based on clinical observations made on their patients who were being treated with horse serum containing diphtheria antitoxin. A clinical syndrome characterised by fever, lymphadenopathy, cutaneous eruptions, and arthralgias were observed 8 to 12 days after the subcutaneous injections of the horse serum in these patients. Based on this early work by Pirquet and Schick, serum sickness as well as anaphylaxis, hayfever, asthma and autoimmune diseases were identified as having altered reactivity or an ‘allergic response’ in which the immune host mediates clinical disease [34, 35]. Kojis (1942), Weaver (1909) and Hunt (1932) confirmed the observations by von Pirquet and Schick with large retrospective clinical studies but it was not until the work by

Germuth (1953) and Dixon et al (1961) that circulating immune complexes and complement activation were shown to be important in the pathophysiology of serum sickness [34].

How the complement system and neutrophils become activated by immune complexes is not completely understood. Some cellular receptors of complement and immunoglobulins, such as C3bR, C5aR and FcγIII have been implicated as important participants in this activation mechanism [33]. In serum sickness, laboratory analyses show elevated erythrocyte sedimentation rate, leukocytosis occasionally accompanied by eosinophilia, haematuria, proteinuria and decrease in complement components in serum (e.g. C3, C4 and CH50 activity). In a recent study, it was found that, after antivenom administration, concentration of antibodies in serum towards heterologous immunoglobulins increases from two times to more than 100 times, as compared to the basal values [36].

Serum sickness after antivenom has a delayed onset between 5 and 14 days after its administration, where for several days the immune system of the patient recognizes the heterologous horse antibodies/proteins as foreign and mounts an IgG-mediated antibody response [33, 37]. While there is clinical evidence suggesting that no sensitization is produced in patients after repeated administration of Fab ovine antivenoms [38], it has been demonstrated that, in the case of whole IgG antivenoms, and possibly for $F(ab')_2$ antivenoms as well, the incidence of late reactions increases with the total amount of heterologous protein administered [39]. This is similar to much earlier work by Black and Gunn who found that serum sickness was much more likely to occur in persons receiving a large volume of botulinal serum antitoxin compared to those receiving a small amount [40]. Thus, antivenom protein concentration and dose appear to be key determinants for the generation of late adverse reactions.

Criteria used to determine the presence of serum sickness in affected patients varies for antivenom type and geographical location. Early investigations by Trinca (1963) [41], where specific Australian or Papua New Guinean monovalent antivenoms were used, and by Campbell (1967) [42], where primarily New Guinea Death Adder and Polyvalent antivenoms were used, did not specify any criteria for diagnosing serum sickness, but did mention that around 7% of their patients had late reaction symptoms consistent with serum sickness. Five independent studies from the United States by Dart *et al* [43], Ruha *et al* [44], Bush *et al* [45], and Lavonas *et al* [46, 47] investigating the effects of Fab antivenom, used serum sickness criteria of rash/urticaria with one of fever, myalgia, epigastric pressure, thrombocytopenia, anorexia, hives, or arthralgia. These studies reported an incidence of serum sickness ranging from 5% to 23%. In a sixth study from the United States on Antivenin (Crotalidae) Polyvalent (ACP) antivenom, LoVecchio used the three symptoms of fever, arthralgia and pruritus (itching) for determining serum sickness, and reported a much higher incidence of 56% of patients developing serum sickness [39]. As these studies show there is no uniform consensus on the symptoms required for a diagnosis of serum sickness due to snake antivenom. This needs to be addressed in future investigations.

Treatment of Serum Sickness

Recommendations on the treatment of serum sickness also vary. Dart and McNally advise that serum sickness may temporarily disrupt patients' activities, such as the ability to work, and often requires symptomatic therapy with antihistamines and systemic administration of steroids [37]. The most current recommendations on treatment come from Isbister, who advises that serum sickness should be treated with a one-week course of corticosteroids, and when greater than 25mL of antivenom is administered it is advisable to give a prophylactic

course of oral corticosteroids [48]. In a Cochrane review on interventions for preventing reactions to snake antivenom, data were reviewed up until March 2004. The authors found that it had not been assessed whether corticosteroids could prevent adverse effects of horse serum antivenom, and that based on the evidence available, corticosteroid treatment was only likely to be of benefit for treating late reactions such as serum sickness. Pirquet and Schick in their early investigations on serum sickness had also discovered that a second, subsequent injection of serum leads to a drop in the amount of circulating antibodies and an increased onset of symptoms. The reaction was found to be specific, because using a different serum for the second injection did not incite the same accelerated response [34]. It has therefore been previously recommended that treatment begins with discontinuing the offending agent, and future avoidance is imperative. Supportive care may be sufficient in mild cases, and antihistamines and non-steroidal anti-inflammatory drugs have been reported to be helpful in childhood serum sickness [49]. In severe cases, oral prednisone appears to be the treatment of choice, starting with a dose of 60mg/day and tapering over two or more weeks to avoid rebound [50]. A randomised controlled trial investigating the effectiveness of corticosteroid treatment compared to placebo for serum sickness is necessary to confirm these recommendations.

Conclusions

The high rate of acute adverse reactions to antivenom is an example of how poor manufacturing and quality control by antivenom producers cause problems for patients and their doctors. This highlights the importance of addressing issues related to poor quality and potentially unsafe antivenom. Ultimately, the prevention of reactions will depend mainly on improving the quality of antivenom. Until these improvements take place, doctors will have to depend on pharmacological prophylaxis as well as careful observation of patients receiving

antivenom in preparation for prompt management of acute as well as delayed reactions when they occur.

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Table 1: Treatment of early antivenom reactions and anaphylaxis consistent with the World Allergy Organisation Anaphylaxis Guidelines

Mild immediate antivenom reactions: (rash, flushing, gastrointestinal effects)
Some mild reactions resolve with temporary cessation of the antivenom infusion and recommencing it at a slower rate.
Severe Anaphylaxis (sudden hypotension, bronchospasm): Initial management
1. Suspend the antivenom infusion.
2. Lie the patient flat (if not already), commence high flow or 100% oxygen and support airway and ventilate patient as required.
3. Commence a rapid infusion of 1000ml Normal Saline (20 mL/kg in children) over 2 to 3 minutes.
4. Administer adrenaline i.m. into the lateral thigh, 0.01 mg/kg to maximum of 0.3 mg (alternatively, those experienced with i.v. adrenaline infusions may proceed directly to this, as below*).
Severe Anaphylaxis: Unresponsive to initial management:
1. If hypotensive, repeat Normal Saline bolus as above (up to 50 mL/kg may be required).
2. Commence i.v. infusion of adrenaline (0.5-1 mL/kg/hour, of 1 mg in 100 mL) and titrate according to response; monitor blood pressure every 3 to 5 minutes; beware that as the reaction resolves adrenaline requirements will fall, the blood pressure will rise and the infusion rate will need to be reduced.
3. Consider nebulised salbutamol for bronchospasm, nebulised adrenaline for upper airway obstruction, and i.v. atropine for severe bradycardia.

* Envenomed patients may be severely coagulopathic, so it is important to be cautious when giving adrenaline to avoid blood pressure surges, which might lead to intracerebral haemorrhage.