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Dealing with adverse reactions to snake antivenom

Snakebite is a global problem with an estimated 421,000 to 1.8 million bites and up to 94,000 deaths each year; the vast majority of patients affected are from South and South East Asia, Sub-Saharan Africa, Central and South America [1]. Systematic reporting of snakebite related mortality and morbidity remains poor especially in areas with the highest snakebite burden. The estimated number of snakebite deaths in India alone is a staggering 45,900 a year, a figure that is 30 fold higher than what is officially reported [2].

Treating snakebite is not a pleasant experience. Most doctors serving in countries with a high snakebite burden dread the experience of having to rescue patients from potentially life threatening complications of envenomation and, in addition, having to treat antivenom-induced adverse reactions; these can occur in up to 75% of patients (severe in 40%) who receive antivenom in some countries [3]. The medical implications for use of antivenoms associated with such a high rate of adverse reactions are not without consequence: the early use of antivenom is frequently discouraged at some rural hospitals allowing time for serious complications of systemic envenoming to develop and become well established.

Allergic reaction, hypersensitisation, and sensitisation, are all terms implying that early anaphylactic reactions to antivenom result from sensitisation from prior exposure to serum proteins of animals from which the antivenom is derived. For these diagnostic terms to be used correctly, type 1 hypersensitivity (immediate hypersensitivity) must be confirmed by evidence of specific IgE-mediation. Skin testing has been used historically to predict such reactions. However, this method is poorly predictive of early adverse reactions to antivenom [4,5].

The majority of antivenom reactions have nothing to do with acquired hypersensitivity or IgE. They are associated with complement activation, which is likely to be initiated by the presence of aggregates of IgG and its antibody fragments, non-specific protein aggregates, or osmotic effects resulting from the intravenous administration of a large bolus-dose of antiserum protein [6,7]. The venom-specific IgG present in horse serum binds snake venom via the Fab (antibody binding fragment) portion of the immunoglobulin leaving the Fc (complement binding fragment) portion directed against the cell surface. The Fc portion is responsible for activation of complement and binding to inflammatory cells through class-specific receptors. Activation of complement leads to the stimulation of complement component receptors, C3a and C5a. Both of these receptors can trigger histamine release from mast cells and increase capillary vascular permeability. It is thought that there is a dose-response relationship with the escalation of antivenom doses (increased immunoglobulin protein delivered) and the increased likelihood of adverse reactions. Furthermore, a dose-dependent relationship for the potential of an

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adverse reaction may exist for any specific antivenom. These dose relationship concepts have been evidenced by reports of high reactogenicity in severely envenomed patients following treatment with increased doses of antivenom [8-9]. Pre-formed histamine present in mast cells can also be released by interaction with some chemicals, independent of complement activation. Histamine has many actions on multiple organ tissues. It causes vasodilatation of small blood vessels with a reduction of peripheral resistance and a consequent fall in blood pressure. It also causes constriction of smooth muscles such as the bronchial smooth muscles. Such complications can occur within seconds or minutes of antivenom infusion. Patients begin to feel a burning-itching sensation, predominantly in the palms, face, scalp and ears. This is soon followed by intense warmth. The skin becomes reddened and the erythema rapidly spreads over the torso. Blood pressure falls and the heart rate accelerates in a compensatory response. These symptoms may further progress to profound hypotension and bronchoconstriction, and progress to shock in severe cases.

It, therefore, becomes apparent that to minimize or prevent adverse or allergic reactions to antivenom the following should be considered: 1) the antivenom preparation should be free of aggregates of IgG, its sub-fraction aggregates, or non-specific protein aggregates, 2) prevention of complement activation is important in order to reduce untoward reactions, and 3) the prevention of downstream effects of complement activation such as cytokine release, and counteracting effects of such release are needed to halt the manifestations of complement activation.

Three classes of drugs are currently used in attempts to prevent antivenom-induced adverse reactions, namely, adrenaline (epinephrine), steroids, and antihistamines. Most of the clinical features of antivenom reactions are mediated by activation of histamine H1 receptors. Therefore, H1-receptor antagonists (true antihistamines) are effective in controlling itching and oedema while their therapeutic actions on bronchodilatation and hypotension are minimal. A study by Fan *et al*. showed that premedication with intramuscular antihistamine (promethazine) does not prevent antivenom-induced allergic reactions [10]. However, antihistamines should be given if and when symptoms of allergic reaction, such as itching are observed.

Gluccorticoids, such as hydrocortisone have not only the ability to inhibit early phenomena of inflammatory processes such as oedema, capillary dilatation, migration of leukocytes to the inflamed area and phagocytic activity, but also reduce the latent manifestations of serum sickness. A single dose of cortisol produces a 70% drop in circulating lymphocytes and a 90% reduction in monocytes within approximately 4-6 hours, and has an effect lasting 24 hours. Therefore, steroids are unlikely to prevent early reactions to antivenom. Gawarammana *et al.*, failed to demonstrate a beneficial effect of premedication using a concurrent infusion of hydrocortisone and antivenom [11]. However, results of another study, using historical controls, suggests that steroid premedication combined with slow administration of diluted antivenom might reduce the frequency and severity of reactions [12]. It is difficult to differentiate whether the reason for reduced reactions was due to the steroids, the slow infusion rate or the dilution of the antivenom.

Adrenaline (epinephrine) is a potent stimulator of both alpha (α) and beta (β) receptors. Its predominant actions are increasing blood pressure and bronchodilatation. Adrenaline can inhibit the mediation of mast cell secretion via stimulation of $\beta 2$ receptors. The first ever randomised, placebo controlled, clinical trial attempting prophylaxis for antivenom-related reactions by Premawardhena *et al.* [13] showed that low dose subcutaneous adrenaline significantly reduced acute adverse reactions to antivenom from 43% to 11%. However, the study was small (105 patients) and could not firmly establish

the safety of adrenaline. Recently, de Silva *et al*. [3], in a study of 1007 patients who received antivenoms currently being used in Sri Lanka, reports that using low-dose subcutaneous adrenaline (0.25 ml, 1:1000 solution) for prophylaxis is both effective and safe, and recommends its use especially in countries where adverse reactions to antivenoms are frequent. Adrenaline reduced the rate of severe adverse reactions compared with placebo by 43% at 1 hour (OR 0.57, 95% CI 0.43-0.75) and by 38% over 48 hours (OR 0.62, 0.51-0.74). This study also demonstrated that neither hydrocortisone nor promethazine had any significant effect on reducing the risk of severe adverse reactions at 1 or 48 hours. It is worthwhile pointing out here that adrenaline is also the drug of choice in treating antivenom reactions once they occur.

Absorption of subcutaneously administered adrenaline is slow owing to the drug's local vasoconstrictive action. There is a moderate increase in systolic pressure owing to vasoconstrictor action; however, peripheral resistance decreases owing to the dominant action on β2 receptors of blood vessels in skeletal muscle, where blood flow is enhanced. As a result there is a net decline in diastolic pressure. Consequently, the mean arterial blood pressure is not, as a rule, greatly elevated, and compensatory baroreceptor reflexes do not appreciably antagonise the direct cardiac effects. Importantly, all of these drugs used for prophylaxis have potential adverse effects, particularly hydrocortisone and adrenaline. The study by de Silva *et al*. [3], showed a significantly higher number of deaths among those who received hydrocortisone compared to no hydrocortisone (ten [2%] versus three [0.6%]; OR 3.3, 95% CI 1.28-8.52) [3]. With adrenaline, the balance of benefit over harm when given prophylactically varies with the baseline risk of developing the adverse reactions. Prophylactic use of subcutaneous adrenaline appears safe, as no serious adverse events were reported by de Silva *et al.* [3] or in previous studies [14,15]. Adverse reaction rates have been known to vary between different brands of antivenom due to different manufacturers' procedural differences and between different batches of the same brand of antivenom due to production process variability. These factors need to be taken into account when assessing the generalisability of trials on prophylaxis against adverse reactions.

The risk of early anaphylactic reactions from the use of antivenom preparations that contain impurities with antibody/protein aggregates or multimers is the primary reason why their use can be dangerous. Modification of antivenoms by enzymatic digestion with papain, pepsin or caprylic acid which cleaves IgG, followed by Fc removal can reduce the potential for acute antivenom reactions. A recent study by León *et al.* [16] demonstrated that the use of beta-propiolactone and quaternary ammonium membranes in antivenom preparation significantly reduced in-vitro anti-complement activity of caprylic acid-fractionated equine antivenom.

The urgent requirement for high quality antivenoms begs the need for further refinements in antivenom preparations and their production. What most countries with high snakebite burdens need is highly purified, polyspecific antivenoms with low reaction rates directed against the medically important, native venomous snake species. The recent WHO guidelines on production, control and regulation of antivenom are, therefore, very timely [17]. Until, such refined antivenoms become available, the use of premedication with subcutaneous adrenaline should be considered to prevent reactions to currently available antivenoms that are known to cause high rates of adverse reactions. However, it must be remembered that even well manufactured antivenom may be associated with severe reaction rates of up to 5% [18]. Therefore, the need for careful observation of patients receiving antivenom and prompt treatment of acute reactions when they occur cannot be over emphasised.

References

1. Kasturiratne A, Wickremasinghe AR, de Silva N, *et al*. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. *PLoS Medicine* 2008; **5**: e218.
2. Mohapatra B, Warrell DA, Suraweera W, *et al*. Snakebite mortality in India: a nationally representative mortality survey. *PLoS Neglected Tropical Diseases* 2011; **5**: e1018.
3. de Silva HA, Pathmeswaran A, Ranasinha CD, *et al*. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. *PLoS Medicine* 2011; **8**: e1000435.
4. Cupo P, Azevedo-Marques MM, de Menezes JB, Hering SE. Immediate hypersensitivity reactions after intravenous use of antivenin sera: prognostic value of intradermal sensitivity tests. *Revista do Instituto de Medicina Tropical de São Paulo* 1991; **33**: 115-22.
5. Malasit P, Warrell DA, Chanthavanich P, *et al*. Prediction, prevention, and mechanism of early (anaphylactic) antivenom reactions in victims of snake bites. *British Medical Journal (Clin Res Ed)* 1986; **292**: 17-20.
6. Day NK, Good RA, Wahn V. Adverse reactions in selected patients following intravenous infusions of gamma globulin. *American Journal of Medicine* 1984; **76**: 25-32.
7. Sutherland SK. Serum reactions. An analysis of commercial antivenoms and the possible role of anticomplementary activity in de-novo reactions to antivenoms and antitoxins. *Medical Journal of Australia* 1977; **1**: 613-5.
8. Malasit P, Warrell DA, Chanthavanich P, *et al*. Prediction, prevention, and mechanism of early (anaphylactic) antivenom reactions in victims of snake bites. *British Medical Journal* 1986; **292**: 17-20.
9. Chippaux JP, Boyer L. The 3 + 3 dose escalation design is not appropriate for antivenom dose finding. *Toxicon* 2010; **55**: 1408-1409; author reply 1410-11.
10. Fan HW, Marcopito LF, Cardoso JL, *et al*. Sequential randomised and double blind trial of promethazine

prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. *British Medical Journal* 1999; **318**: 1451-2.

11. Gawarammana IB, Kularatne SA, Dissanayake WP, *et al*. Parallel infusion of hydrocortisone +/- chlorpheniramine bolus injection to prevent acute adverse reactions to antivenom for snakebites. *Medical Journal of Australia* 2004; **180**: 20-3.
12. Caron EJ, Manock SR, Maudlin J, *et al*. Apparent marked reduction in early antivenom reactions compared to historical controls: was it prophylaxis or method of administration? *Toxicon* 2009; **54**: 779-83.
13. Premawardhena AP, de Silva CE, Fonseka MM, *et al*. Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. *British Medical Journal* 1999; **318**: 1041-3.
14. Dassanayake AS, Karunanayake P, Kasturiratne KT, *et al*. Safety of subcutaneous adrenaline as prophylaxis against acute adverse reactions to anti-venom serum in snakebite. *Ceylon Medical Journal* 2002; **47**: 48-49.
15. Kularatne SA, Gawarammana IB, Kumarasiri PV, *et al*. Safety and efficacy of subcutaneous adrenaline as a treatment for anaphylactic reactions to polyvalent antivenom. *Ceylon Medical Journal* 2003; **48**: 148-9.
16. Leon G, Lomonte B, Gutierrez JM. Anticomplementary activity of equine whole IgG antivenoms: comparison of three fractionation protocols. *Toxicon* 2005; **45**: 123-8.
17. WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins. Geneva: WHO, 2010. http://www.who.int/bloodproducts/snake_antivenoms/snakeantivenomguide/en/index.html
18. Isbister GK, Brown SGA, MacDonald E, White J, Currie BJ. Australian Snakebite Project Investigators. Current use of Australian snake antivenoms and frequency of immediate-type hypersensitivity reactions and anaphylaxis. *Medical Journal of Australia* 2008; **188**: 473-6.

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