Antivenom, anecdotes and evidence

Envenoming is rare in Australia — multicentre studies are needed to improve the tenuous evidence base

Whether it's the live snake that escapes in an emergency department or the farmer, bitten by a brown snake, who drops into his wife's work to say he will be in hospital, and then collapses and has a seizure on arriving in hospital — bites and stings are a fascinating topic and the occasional envenoming presenting to hospital makes the local news. Unfortunately, the rarity of envenoming in Australia has meant the evidence base in clinical toxinology is tenuous, with considerable reliance on case reports and anecdotes of successful treatment. Although case reports can be essential in providing information about rare effects, more importantly they help to develop hypotheses for further studies.

Randomised controlled trials (RCTs) of antivenoms are difficult to undertake in clinical toxinology because of the rarity of envenoming, the rapid course of life-threatening effects, and the potential for complete reversal of effects with antivenom. Funnel-web spider envenoming and major box jellyfish envenoming by *Chironex fleckeri* are two contrasting examples of such situations, with very different outcomes over the past 30 years following the introduction of their respective antivenoms.

Despite the absence of an RCT of funnel-web spider antivenom, most people would agree that its introduction has prevented death in some cases and changed the outcome in many more cases over the past 25 years. It is highly unlikely that any ethics committee would now sanction an RCT, except perhaps to conduct a short *n*-of-1 trial, randomising patients initially to antivenom or placebo, and providing rescue treatment after 1–2 hours.[1] The initial prospective study of nine successfully treated patients,[2] another study demonstrating a significant reduction in hospital length of stay,[3] as well as the fact that there have been no fatal bites since the introduction of funnel-web spider antivenom, provide more than single-case or anecdotal evidence for its efficacy.

In contrast, the introduction of *C. fleckeri* antivenom has been somewhat different, with reported deaths despite the administration of antivenom, and continuing controversy about its use intramuscularly in the prehospital setting and in treating non-life-threatening effects.[4] Recent animal work suggests that pretreatment with antivenom is not completely effective in preventing cardiovascular collapse and adds to the concerns regarding the efficacy of this antivenom.[5]

Irukandji syndrome has come to the attention of most Australians over the past few years, with at least one confirmed death from Irukandji syndrome in far north Queensland,[6] and reports of significant numbers of cases in northern Western Australia in this issue of the Journal (*page 699*).[7] This has attracted significant media attention, threatened tourism in Queensland, and prompted the rapid introduction of untested treatments.[8] Unfortunately, this appears to have overshadowed the far more lethal *C. fleckeri* envenoming, which continues to claim lives, with recent deaths of young children in far north Queensland. Treatment for *C. fleckeri* envenoming remains controversial, with concerns about the efficacy of antivenom,[4] disagreement over the role of pressure immobilisation bandaging[9] and non-evidence-based ongoing support for the potentially dangerous adjunctive treatment with verapamil.[10]

Recent animal studies provide evidence that pressure bandaging in *C. fleckeri* envenoming may increase venom discharge,[11] and a review of the literature found no evidence for the recommendation of pressure immobilisation in major jellyfish stings.[9] A recent animal study investigating treatments for *C. fleckeri* envenoming demonstrated that pretreatment with antivenom only prevented cardiovascular collapse in 40% of rats.[5] The addition of verapamil did not prevent any deaths, supporting previous studies showing that verapamil worsens outcome in *C. fleckeri* stings.[12] Another finding was that the addition of intravenous magnesium sulfate to antivenom, as a pretreatment, prevented death in 100% of cases.[5] Future studies will need to further evaluate antivenom and the possible benefits of magnesium. However, it must be emphasised that early resuscitation is likely to be the single most important measure in severe *C. fleckeri* envenoming.

Back on land, Australia is extremely fortunate to have some of the safest and most efficacious snake antivenoms in the world and the only commercially available snake venom detection kits for patient management. Despite this, the management of snakebite continues to be dominated by anecdotes and case reports, with limited information on antivenom dosing and redose timing. In addition, many snakebites occur in rural or remote areas, necessitating use of retrieval services and telephone advice.

In this issue of the Journal, Yeung et al (*page 703*) report a retrospective study of severe brown snake envenoming in Western Australia, suggesting that larger overall doses of antivenom are required.[13] Although the authors have moved to using 10 ampoules as their initial dose, their study does not provide conclusive evidence to allow absolute recommendations for antivenom dosing, particularly in other parts of Australia. However, it reinforces the problems with severe brown snake envenoming in rural and remote areas, and the need for sufficient antivenom being available for a first dose (at least five ampoules) for patients with suspected snakebite being retrieved to larger centres.

The study by Yeung et al[13] also provides the impetus for prospective studies of snakebite to define the initial antivenom dose and the need for further doses. Such studies are only possible if there is serial estimation of venom concentrations in blood to determine the antivenom dose required to completely neutralise circulating venom.[14] Because of the rarity of snake envenoming, a multicentre study is required.

The study by Currie (*page 693*) demonstrates just how uncommon snakebite envenoming is in Australia.[15] Despite enrolling patients at a hospital that has large numbers of snakebite presentations, the study period required was about 10 years. Multicentre studies are currently being conducted throughout Australia, with collaborative research between clinical toxinologists and emergency physicians in more than 30 hospitals. In addition to answering questions about antivenom dosing, these studies will prospectively evaluate the effectiveness of pressure bandaging with immobilisation.

Many questions remain about the use of snake antivenom. The treatment of and premedication to prevent snake antivenom

reactions is still of concern. There have been three RCTs,[16,17] but because of problems with small numbers and methodology[18] many questions remain. Such studies are difficult in Australia because of the infrequency of administration of antivenom in single centres. Again, we need either large multicentre studies or, alternatively, studies conducted in rural tropical countries such as Papua New Guinea or Sri Lanka, where snakebite envenoming is common and a major public health issue. Collaborative work between these countries and Australia will both improve the care of patients and contribute to our understanding of snake antivenoms.

Geoffrey K Isbister
Clinical Toxicologist, Newcastle Mater Misericordiae Hospital and Conjoint Senior Lecturer, University of Newcastle, Newcastle, NSW
gsbite@ferntree.com

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