
Available from: http://dx.doi.org/10.1093/qjmed/hcs132

Accessed from: http://hdl.handle.net/1959.13/1045427
Bites in Australian snake handlers - Australian snakebite project (ASP-15)

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Number of Figures:

Number of Tables:

Funding: The study was supported in part by NHMRC Project Grant ID490305. GKI is supported by an NHMRC Clinical Career Development Award ID605817. SGAB is supported by NHMRC Career Development Fellowship Award ID1023265.
Abstract

Background: Snakebites in snake handlers are an important clinical problem that may differ to bites in the general population.

Aim: To investigate the epidemiology and clinical presentation of bites in snake handlers.

Design: Prospective observational study.

Methods: Bites in snake handlers recruited as part of the Australian Snakebite Project (ASP) from 2004 to 2011 were included in the study. Data were extracted from the ASP database, which included demographic and clinical information, laboratory tests and antivenom treatment.

Results: From 1089 snake bites recruited to ASP, there were 106 (9.7%) bites in snake handlers. The median age was 40 years (Range: 16-81yr) and 104 (98%) were males. The commonest circumstances of the bites were handling snakes (47), catching snakes (22), feeding snakes (18) and cleaning cages (11). Bites were to the upper limb in 103 cases. Bites were most commonly by Red-bellied black snakes (20), Brown snakes (17), Taipan (15), Tiger snakes (14) and Death adders (14). Envenoming occurred in 77 patients: venom-induced consumption coagulopathy in 45 patients (58%), neurotoxicity in 10 (13%) and myotoxicity in 13 (17%). Systemic hypersensitivity reactions to venom occurred in eight, satisfying clinical criteria for anaphylaxis in five, of which three were hypotensive. Antivenom was administered in 60 envenomed patients. Systemic hypersensitivity reactions to antivenom occurred in 15 (25%; 95% CI: 15-38%), including 2 (3%; 1-13%) with severe (hypotensive) reactions.
Conclusion: Bites in snake handlers remain a common, important problem and involving a broad range of snakes. Neurotoxicity and myotoxicity are relatively common, consistent with the snakes involved. Venom anaphylaxis was common, despite previously being a poorly recognised problem in snake handlers. The incidence of systemic hypersensitivity reactions to antivenoms, including anaphylaxis, was not higher than that observed in non-snake handlers.
1. Introduction

Snake bite is now recognised as a global public health issue in tropical and subtropical countries.\(^1\) In many developed countries where snake envenoming is not a major health issue, it is an occupational health hazard for snake handlers. Although there are numerous cases and case series of exotic snake bites,\(^2\) this is usually by non-native snakes and occur in zoos/reptile parks or in private collectors. The major issues in these cases, is access to information on the effects of envenoming by the snake and obtaining the correct antivenom.

In Australia, private collectors and herpetologists tend to collect Australian snakes rather than exotic snakes from other countries. In a small series of 28 herpetologists and amateur snake handlers from Queensland sustaining 119 bites, all bites were from Australian snakes.\(^7\) Although the management of these patients is the same as any person bitten by an Australian snake, there are potential problems with repeated exposure to snake venom and repeated use of antivenom.

The treatment of a snake handler can be difficult because they usually know more about snakes than the treating clinician and have strong opinions on the treatment of snake bite. However, there is potential misinformation about the treatment of snake bite in the herpetology community. There is almost no published information on the differences in the treatment of snake handlers to the normal population.

Many herpetologists and snake handlers do not want to receive antivenom unless they have severe envenoming. There is a belief that snake handlers are at a higher risk of immediate hypersensitivity reactions compared to the normal population. There is little published data to support this premise and studies of immediate hypersensitivity reactions rarely consider this as a risk factor.\(^8,\)\(^9\)
A potentially more serious concern is the risk of immediate hypersensitivity reactions to snake venom, because the human immune system probably evolved to respond via allergic immune pathways to venoms and other noxious substances. Anaphylaxis has been reported in both snake handlers and in laboratory researchers working with venom. However, there is limited information on how common this is and the type of reactions that occur.

The aim of this study was to investigate the epidemiology and clinical presentation of snake bites and envenoming in snake handlers, with particular reference to systemic hypersensitivity reactions (SHSR).
2. Materials and Methods

2.1 Materials

Pooled snake venom was obtained from Venom Supplies, Tanunda, South Australia. All antivenoms were purchased from CSL Ltd. Bovine serum albumin (BSA), Tetramethylbenzidine (TMB) and rabbit anti-horse IgG peroxidise conjugate were purchased from Sigma. Rabbit anti-snake antibodies were obtained from the Western Australian Institute of Medical Research. Anti-\textit{P. textilis} IgY was a gift from Frank Madaras and was biotinylated using EZ-Link Sulfo-NHS-LC-Biotin from Pierce. Other laboratory reagents of analytical grade included phosphate buffered saline (PBS), sulphuric acid and streptavidin-conjugated horseradish peroxidase (HRP) obtained from Millipore.

2.2 Design and Setting

This was a prospective study of definite snake bites in snake handlers recruited to the Australian snakebite project (ASP). ASP prospectively recruits snake bite patients from over 100 Australian hospitals including referrals from the National Poison Information Centre Network. The design, patient recruitment and data collection are described in detail elsewhere.\textsuperscript{15} Approval from Human Research and Ethics Committees covering all involved institutions was obtained.

2.2.1 Patients

All snake handlers recruited to ASP between 2004 and 2011 were included in this study. Snake handlers included any person who collects or keeps snakes privately, works in a zoo or reptile-park, works with snakes, or undertakes research on snakes. Identification of the snake was either by expert identification by the patient or by
venom-specific enzyme immunoassay (EIA) for the major groups of venomous snakes (Brown snake, Tiger snake, Rough-scaled snake, Mulga snake, Red-bellied black snake, Death Adder, Taipan and Hoplocephalus spp.).

A second cohort of patients with snake envenoming but who were not snake handlers was extracted from the ASP database to compare antivenom reactions and allergic reactions to snake venom.

### 2.2.2 Data and sample collection

Patient demographics, clinical effects, laboratory results, treatment and clinical outcomes were extracted from the ASP database. Data was extracted for all cases involving a snake handler and classified into envenomation syndromes: venom induced consumption coagulopathy (VICC; complete or partial), neurotoxicity, myotoxicity, thrombotic microangiopathy (TMA) and systemic symptoms, as previously described.\(^{16}\) Antivenom treatment, complications and adverse events were also extracted. SHSR to antivenom were defined as anaphylaxis if they met NIAID-FAAN consensus criteria for this diagnosis,\(^{17}\) and defined as severe according to the grading system developed by Brown.\(^{18}\) Clinical data for adverse events were originally taken from purpose-designed Adverse Reaction forms returned by the treating clinicians. That included Yes/No options for major allergic symptoms, and clinical observations including baseline and reaction blood pressures. SHSR were defined as an new onset allergic symptom affecting the skin, respiratory, cardiovascular or gastrointestinal systems, SHSR that occurred after the bite and prior to antivenom were assumed to be reactions to snake venom. Serum is collected from all patients recruited to ASP, centrifuged and stored at -80°C for measurement of venom concentrations.
2.3 Enzyme immunoassay

Materials and methods for this EIA have previously been described (Kulawickrama et al., 2010; O’Leary, et al., 2006). Briefly, 96 well plates were coated overnight with rabbit anti-snake venom antibodies. The next day, following PBS washes and blocking with 0.5% BSA, one-in-ten diluted patient serum was applied in triplicate to the wells, with and without the corresponding antivenom. The plates were incubated at room temperature for one hour, then washed with PBS. Biotinylated anti-snake venom IgG was then added to the wells for an hour, then washed, before applying Streptavidin HRP. The final step involved adding TMB and sulphuric acid prior to reading the plates at 450nm on a plate reader.

Anti-snake venom IgG was available for Tiger snake (*Notechis* spp.), Rough-scaled snake (*T. carinatus*), Mulga snake (*Pseudechis australis*), Red-bellied black snake (*P. porphyriacus*), Death Adder (*Acanthophis* spp.), Taipan (*Oxyuranus* spp.) and *Hoplocephalus* spp. For Brown snake (*Pseudonaja* spp.) anti-snake venom IgY was used instead of anti-snake venom IgG. The limit of detection for the snake venom concentration ranged from 0.15 to 0.2ng/ml.

2.4 Data analysis

Continuous data is reported with medians, interquartile ranges (IQR) and ranges, and proportions were reported with 95% confidence intervals (CIs). For EIAs standard curves were fitted by linear and non-linear regression using both Excel and Prism 5.03 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.
Results

From 1089 snake bites recruited to ASP, there were 106 (9.7%) bites in snake handlers, including three patients bitten on three different occasions and seven patients bitten on two occasions. In addition, there were two children bitten by their parents’ snakes. A 2 year old boy was bitten by his parent’s Collett’s snake and was treated with antivenom for myotoxicity. A 9 year old was bitten by a Stephen’s banded snake collected by his father and was treated with antivenom for VICC. Seventy seven of the 106 patients were envenomed.

3.1 Demographics

Demographics of the 106 snake handlers are summarised in Table 1. Cases occurred in all States and Territories of Australia except the Australian Capital Territory. The median age was 40 years (Range: 16 to 81 years) and 104 (98%) were males. The commonest circumstances of the bites were handling snakes (47), catching snakes (22), feeding snakes (18), cleaning cages (11), medicating snakes (2) and milking a snake (1). In only two cases was the patient not interfering with the snake. Alcohol was involved in 7 cases (7%).

Most patients (103; 96%) were bitten on their upper limb, 52 on the finger. Ninety nine bites (93%) were from potentially venomous Australian snakes (Table 2) based on expert identification or venom specific enzyme immunoassay.

3.2 Clinical effects

The clinical effects in the 77 envenomed patients are summarised in Table 3. VICC occurred in 47 patients (58%), neurotoxicity in 10 (13%) and myotoxicity in 13 (17%).
Eight patients (10%) had an allergic reaction to snake venom. All had been previously bitten and envenomed by a venomous Australian snake except for one patient who regularly milked venomous snakes. Four of the eight had no evidence of major systemic envenoming, two had VICC and two had partial VICC. Three had mild (skin-only) SHSR and five had reactions satisfying the NIAID-FAAN clinical definition for anaphylaxis and three of these were severe, with hypotension. In one patient who presented with hypotensive anaphylaxis, the diagnosis was not made and the patient was treated with antivenom rather than adrenaline. They slowly recovered with only fluid resuscitation and the diagnosis was only considered after they developed only a very mild coagulopathy.

3.3 Snake Venom Detection Kit (sVDK) results

A bite site sVDK was done in 65 of 106 patients and was correct in 56 patients (86%). In five cases the snake was non-venomous or the patient was not envenomed. In one case brown snake antivenom was given incorrectly for envenoming by an Inland Taipan. In one case polyvalent antivenom was given for a Pale-headed snake bite which would usually receive the lower volume tiger snake antivenom. In two cases the correct antivenom was given despite the sVDK result.

3.4 Antivenom

Antivenom was given in 60 of the 77 envenomed patients. Of the seventeen not given antivenom, 11 were envenomed by red-bellied black snakes, 3 had mild envenoming (tiger, brown and death adder), two had venom allergy and one presented 8 days after the bite. SHSR and anaphylaxis to antivenom occurred in 15/60 (25%) and 7/60(12%) respectively in snake handlers, compared to 77/410 (19%) and 27/410(6%) respectively in non-snake handlers, a difference that was not statistically significant.
(Table 4 and 5). One non-envenomed patient was given polyvalent antivenom and did not have a reaction.
4. Discussion

This study provides insight into bites in snake handlers who are likely to have had previous exposure to snakes, and in some cases, previous snake bites and snake envenomings. Almost all bites were in males on the upper limb and involved handling the snake. The spectrum of clinical effects in snake handlers differed to all snake envenoming in Australia, with only slightly more than half of cases developing VICC, and neurotoxicity and myotoxicity occurring more commonly. This is likely a reflection of the difference in the range of snakes involved, with less brown snake compared to snakes causing neurotoxicity (death adder and taipan) and myotoxicity (black snakes). An important finding was that SHSR including anaphylaxis to snake venom occurred in 10% of cases and were severe in 3 patients. However, contrary to the popular belief of snake handlers, SHSR to antivenom where similar in frequency and severity to the general Australian population.

All the snakes involved in this study were native Australian snakes rather than exotic snakes. Over the course of the Australian snakebite project the investigators have been aware of bites by exotic snakes, but there were less than five cases that were notified to ASP (Personal Communication, Isbister, G, 2012). Exotic snake bites are not recruited to ASP because they are rare and the aims of ASP are to investigate envenoming by Australasian snakes. Although exotic snake bite appears to be rare in Australia, this study does demonstrate that the types of snakes causing bites in snake handlers differ to bites occurring in the general population from wild snakes. Snakes that are uncommon, more attractive, and potentially easier to look after in captivity, were involved, such as *Hoplocephalus* spp. and Collett’s snake (*P. colletti*) were implicated in this series of bites. In contrast, brown snake envenoming, the most
common important snake envenoming in Australia,\textsuperscript{9} caused less than one fifth of bites in this series. A major advantage of Australian snake handlers being bitten almost exclusively by Australian snakes is that there is no issue with antivenom supplies or finding expertise on the snake involved.

Studies in the United States have much lower rates of bites from captive snakes, with one study reporting only 4 of 73 venomous snake bites occurring from captive snakes.\textsuperscript{19}

The frequency of reactions to snake antivenom was slightly higher in snake handlers (25\% versus 18\%), although this was not statistically significant and the frequency of severe reactions was identical when compared to all other snake envenomed patients (Table 5). The results are confounded by the fact that snake handlers received more large volume antivenoms (death adder, black snake, taipan and polyvalent) that are associated with higher rates of SHSR\textsuperscript{9} compared to other patients who received more of the lowest volume antivenom, brown snake antivenom (Table 4). Larger volumes of foreign protein are more likely to induce SHSR by non-allergic (that is, not immunologically specific) mechanisms.

Our results do not prove beyond any doubt that the risk of developing allergy (antibody-specific reactivity) to antivenoms with repeated dosing is low. However, considering them in context with uncertainty about the mechanisms underlying antivenom reactions, including that IgE-mediated mechanisms have been implied but never proven, should provide reassurance. It is likely that most, if not all, antivenom reactions occur by a variety of non-allergic mechanisms.\textsuperscript{20} Australian snake handlers can be reassured that they are not at a higher risk of severe reactions and so can be safely given antivenom.
Conversely, anaphylaxis to snake venom is a significant risk for snake handlers. A number of previous studies have confirmed that such reactions are likely to be IgE mediated and thus related to prior exposure to either bites of inhalation of dried venom.\textsuperscript{21-23} This may be particularly dangerous if there is a co-existent venom-induced consumption coagulopathy and treatment with adrenaline – which may cause an increase in blood pressure with the potential risk of intracranial haemorrhage.

Bites in snake handlers remain a common and important problem and involve a broad range of snakes that differs from snake bites in the general population from snakes in the wild. More snake handlers developed neurotoxicity and myotoxicity, and allergy and anaphylaxis to snake venom is a major problem that is not well recognised. There was no difference in the rate of severe antivenom reactions between snake handlers and all other envenomed patients receiving antivenom.
Acknowledgements

We thank the numerous medical and nursing staff and local site investigators that have helped recruit patients to the Australian snakebite project. Margaret O’Leary for undertaking enzyme immunoassays for the Australian snakebite project. Renai Kearney for assistance with entering and extraction of data from the ASP database.