Current use of Australian snake antivenoms and frequency of immediate-type hypersensitivity reactions and anaphylaxis

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Antivenom is the mainstay of treatment for snake envenoming. In Australia, snake antivenoms have been available for over 50 years and are regarded as some of the most effective and safe antivenoms. However, there remains significant controversy over the dose required for each monovalent antivenom,[1,2] the specific indications for first and repeat doses, and the frequency and severity of immediate-type and delayed hypersensitivity reactions.[3]

Snake envenoming is rare in Australia, and because of the prevalence of cases in rural and regional Australia, and because no one keeps records of snake bites across Australia, it has been difficult to determine actual numbers of cases each year, the amount of antivenom used, the indications for use and adverse reactions. Previous studies were mainly reviews of spontaneous reporting to CSL Limited (Melbourne, Vic) of antivenom use,[4,5] single-hospital studies or small or poorly designed retrospective studies.[6-9] These studies report reaction rates to antivenom from zero to 54%, and their definitions of anaphylaxis and allergy have not been consistent. These disparate results are problematic, and do not provide useful information for guiding clinical care.

We aimed to investigate the current use of antivenom and immediate hypersensitivity reactions to antivenom in Australia through a multicentre prospective study of snake bites.

METHODS

The Australian Snakebite Project (ASP) is an ongoing multicentre prospective study which recruits cases of snake envenoming from over 60 major tertiary and regional hospitals, as well as referrals to all major Australian poisons centres. Ethical approval for this study was obtained from 16 human research and ethics committees covering all institutions involved in the study.

Patients' demographic information, clinical features of envenoming, laboratory results, first aid and treatments are recorded on a standardised study datasheet. Datasheets are supplied to the treating doctor at the time of the bite, completed by hospital staff and faxed or sent back to the investiga-

ABSTRACT

Objective: To investigate current use of Australian snake antivenoms and the frequency and severity of immediate-type hypersensitivity reactions.

Design: Nested prospective cohort study as part of the Australian Snakebite Project.

Patients and setting: Patients receiving snake antivenom in Australian hospitals between 1 January 2002 and 30 November 2007.

Main outcome measures: The use of CSL Limited antivenom; frequency and severity of hypersensitivity reactions to antivenom; premedication and treatment of these reactions.

Results: Snake antivenom was administered to 195 patients, mostly for venom-induced consumption coagulopathy (145 patients, 74%), followed by non-specific systemic effects (12%), neurotoxicity (5%) and myotoxicity (4%). Antivenom was given to nine patients (5%) without evidence of envenoming or who were bitten by a species of snake for which antivenom is not required. The commonest antivenoms used were brown snake (46%), tiger snake (30%) and polyvalent (11%). The median dose was four vials (interquartile range, 2–5 vials), and 24 patients received two different types of antivenom. Immediate-type hypersensitivity reactions occurred in 48 patients (25%); 21 satisfied our definition of anaphylaxis, with 11 moderate and 10 severe cases, including nine in which patients were hypotensive. The remaining 27 reactions were mild (skin only). Adrenaline was used in 26 cases with good effect. The frequency of reactions to tiger snake (41%) and polyvalent (41%) antivenoms was higher than that to brown snake antivenom (10%). Hypersensitivity reactions occurred in 11 of 40 patients receiving any form of premedication (28%) and in 2 of 11 given adrenaline for premedication (18%) versus 20 of 86 not receiving premedication (23%).

Conclusions: Antivenom was used appropriately, and most commonly for coagulopathy. Hypersensitivity reactions were common, but most were not severe. The discretionary use of premedication was not associated with any reduction in reactions.

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tors. Local investigators at some hospitals maintain datasheets, and complete and fax them back to the chief investigators. Cases of snakebite are recruited mainly in the emergency department or intensive care unit within 24 hours of the bite. A small number of cases (< 5%) are recruited after discharge from hospital, and the same data collection process is used. Faxed datasheets are reviewed by the chief investigators or trained research nurses to check data entry and obtain medical records for missing information. Data are then entered into a purpose-built relational database by G K I. Treatment is decided by the treating doctor, but may be based on advice from a consultant clinical toxicologist contacted about the case.

Here, we describe a nested cohort of patients who received antivenom, in order to report the characteristics of snakebite

patients treated with antivenom, the frequency and severity of immediate-type hypersensitivity reactions to antivenom, and treatment for antivenom anaphylaxis. All patients recruited to the ASP between 1 January 2002 and 30 November 2007 were included if they received CSL snake antivenom. Specific information extracted from our database for this analysis included: patient demographic characteristics; clinical features of envenoming; details of antivenom treatment (type and dose); antivenom hypersensitivity reactions; premedication; and treatment of antivenom reactions. Patients were classified into five groups by a single investigator, based on the type and severity of envenoming as follows:

• Venom-induced consumption coagulopathy, defined as an international normalised ratio (INR) greater than 2.0 *or* prothrombin time (PT) twice normal *or*

1 Grading system for generalised hypersensitivity reactions[10]

Grade*	Description	Definitive features
1	Mild (skin and subcutaneous tissues only)	Generalised erythema, urticaria, periorbital oedema, or angioedema
2	Moderate (features suggesting respiratory, cardiovascular or gastrointestinal involvement)	Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
3	Severe (hypoxia, hypotension, or neurological compromise)	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension (systolic blood pressure, < 90 mmHg in adults), confusion, collapse, loss of consciousness, or incontinence

SpO_2 = oxygen saturation as measured by pulse oximetry.
* The moderate and severe grades approximate the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network definition of anaphylaxis.[11] ◆

fibrinogen level below the lower limit of normal *plus* an elevated D-dimer level.
• Neurotoxicity, defined as at least ptosis and including extra-ocular ophthalmoplegia, bulbar palsy, respiratory muscle paralysis and limb paralysis.
• Myotoxicity, defined by local or generalised myalgia and/or muscle weakness in association with a creatine kinase level > 1000 U/L.
• Non-specific systemic features, defined as at least three of nausea, vomiting, abdominal pain, diarrhoea, diaphoresis and headache.
• No objective evidence of envenoming before the administration of antivenom, or bite by an identified snake for which antivenom is not indicated (eg, whip snake).

Immediate-type hypersensitivity reactions were classified as mild, moderate or severe (Box 1),[10] based on the details recorded for each allergic reaction in the database. If patients received two types of antivenom, only the first antivenom received was analysed because all but two reactions occurred after the first dose of antivenom. Our definition of anaphylaxis was a moderate or severe reaction according to this grading system, which correlates closely with a recent inter-national consensus definition of anaphylaxis.[11] Treatment for each reaction was recorded. For a subgroup of 126 patients treated in larger centres that had an ASP investigator based onsite, hospital notes were available for us to perform a post-hoc analysis of premedication use.

For descriptive statistics, median and interquartile ranges (IQRs) were used for data not normally distributed. Mathematica, version 5.2 (Wolfram Research, Inc, Champaign, Ill, USA) was used for statistical analyses.

RESULTS

CSL snake antivenom was administered to 195 patients recruited to the ASP during the study period of almost 6 years; 90% of these patients received antivenom in the final 3 years of the study because of increased awareness of the study among clinicians leading to a higher recruitment rate. The median age of the 195 patients was 41 years (IQR, 24–52 years), and 152 (78%) were male. The commonest reason for antivenom administration was venom-induced consumption coagulopathy (145 patients; 74%), followed by nonspecific systemic effects (12%), neurotoxicity (5%) and myotoxicity (4%) (Box 2).

Antivenom was given to nine patients (5%) without evidence of envenoming or who were bitten by a species of snake where antivenom treatment is not required. The commonest antivenoms used were brown snake and tiger snake antivenoms (Box 2). The median antivenom dose was four vials (IQR, 2–5 vials). Twenty-four patients received two different types of antivenom — nine were given polyvalent antivenom before the snake was definitively identified, eight were given polyvalent antivenom because there was insufficient monovalent antivenom or it was unavailable, and seven were given the incorrect monovalent (6) or polyvalent (1) antivenom.

Immediate-type allergic reactions occurred in 48 patients (25%); reactions were mild in 27, moderate in 11 and severe in 10 patients (Box 3). The commonest feature was generalised erythema or urticaria (44 patients; 92%). Hypotension (systolic blood pressure < 90 mmHg) occurred in nine of the 10 severe cases. Respiratory manifestations were uncommon, with wheeze in seven patients, stridor in one, and hypoxaemia in three. Adrenaline was used for treatment in 26 cases of immediate-type hypersensitivity reactions (54%). There were no deaths attributed to allergic reactions. Administration of antivenom was not stopped (or was already complete) in 32 cases of reaction, was stopped and restarted or slowed in 11 cases, and was stopped when partially complete in five cases. Reactions of any severity were most common with tiger snake, polyvalent and death adder antivenoms, and severe reactions occurred with all of the three most commonly used antivenoms. There was a statistically significant difference between the frequencies of reactions to different antivenoms (log-likelihood ratio test, $\chi^2 = 23.75$; df = 5; $P = 0.0002$). The reaction occurred after the first dose of antivenom in 46 of the 48 cases and, in the two cases where a reaction

2 Indications for antivenom and types of antivenom used

Major indication	No. of patients	Antivenom used						
		Brown snake	Tiger snake	Black snake	Taipan	Death adder	Polyvalent	Sea snake
Venom-induced consumption coagulopathy	145	83	43	—	5	—	14	—
Non-specific systemic effects	23	2	12	6	—	—	3	—
Neurotoxicity	10	—	—	—	—	9	1	—
Myotoxicity	8	—	2	4	—	—	1	1
No apparent indication/non-envenomed	9	4	2	—	—	—	3	—
Total	195	89	59	10	5	9	22	1

3 Frequency of immediate-type hypersensitivity reactions and anaphylaxis for each snake antivenom

Antivenom	No. of patients receiving antivenom	No. of patients (%) with immediate-type hypersensitivty reactions	Anaphylaxis		
			Mild	Moderate	Severe
Brown snake	89	9 (10%)	3	3	3
Tiger snake	59	24 (41%)	13	5	6
Black snake	10	1 (10%)	—	1	—
Death adder	9	4 (44%)	4	—	—
Taipan	5	1 (20%)	1	—	—
Polyvalent	22	9 (41%)	6	2	1

occurred after a later dose, the patient received only one type of antivenom.

Information was available on premedication use in 126 patients. Forty of these received premedication, with 11 patients receiving adrenaline, 17 receiving promethazine and 27 receiving hydrocortisone. Of these, 11 received both promethazine and hydrocortisone, three received both adrenaline and hydrocortisone, and one was given all three agents. Immediate-type hypersensitivity reactions occurred in 11 of 40 patients receiving any form of premedication (28%), two of 11 patients receiving adrenaline (18%) and 20 of 86 patients who did not receive premedication (23%). Two patients appeared to have immediate-type allergic reactions to venom with clinical effects of allergy manifesting before antivenom administration. Both were snake handlers who had had previous snake bites, and both were bitten by taipans.

DISCUSSION

Antivenom is mainly used in Australia to treat venom-induced consumption coagulopathy, with less than 10% being used for neurotoxicity and myotoxicity combined. Antivenom was used in only a small number of patients without signs of envenoming, suggesting that most antivenom in Australia is being used appropriately. The rate of immediate-type hypersensitivity reactions to antivenom is higher than we would have expected from most previous reports (Box 4), but is consistent with other antivenoms containing $F(ab')_2$ immunoglobulin fragments internationally.[12] Severe reactions were uncommon and characterised mainly by hypotension. Skin reactions occurred in almost all cases and respiratory effects were uncommon. Antivenom therapy was completed in most cases, and there were no fatalities associated with antivenom use. Premedication was administered in a small proportion of patients, but was not associated with a reduction in the reaction rate (although there may have been selection bias as high-risk patients may have been more likely to receive premedication).

The rate of antivenom reactions has varied in previous studies from no reactions being reported in one small retrospective study[6] to 54% and 39% reported in two early studies from Papua New Guinea (Box 4) by Campbell.[13,14] None of these studies clearly defined immediate-type hypersensitivity reactions and, in most, it is difficult to determine the frequency of severe reactions (Box 4).[4-7,9,13-16] The higher rate of any immediate-type hypersensitivity reactions in Campbell's studies may reflect a degree of better ascertainment than other studies, as Campbell observed and managed the patients himself, rather than relying on data from questionnaires or retrospective review of cases.[13,14] Campbell noted that some of the reactions were transient and could only be recorded if the patient was closely observed. The frequency of severe reactions reported by Campbell and others was low,[4,13,14,16] and similar to that in our study.

It is difficult to interpret the differing frequencies of reactions to the various monovalent antivenoms. We have previously reported a high frequency of reactions to tiger snake antivenom,[17] which is supported by this larger study. However, the large difference in frequencies of reactions to tiger and brown snake antivenoms is difficult to reconcile with the fact that the antivenoms are, in fact, polyvalent. This has been confirmed recently in a study showing that brown and tiger snake antivenoms are mixtures, and neutralise and bind to both brown and tiger snake venoms.[18]

The use of premedication was dictated by the treating doctor, and adrenaline, promethazine and corticosteroids were used or in varying combinations. Statistical comparisons between various different premedication regimens was not possible, but there appeared to be no association between adrenaline (alone or in combination) or other premedication and immediate-type

4 Summary of previous studies of acute allergic reactions from Australasian snake antivenoms

Study	Total no. of cases	Study design	Antivenom reaction	Severe anaphylaxis*
Trinca, 1963[4]	100	Retrospective; spontaneous reports of antivenom use	8 (8%)	3 (3%)
Campbell, 1964[13]	39	Unclear methods	21 (54%)	1 (3%)
Campbell, 1967[14]	28	Collection of cases; unclear methods	11 (39%)	1 (4%)
Sutherland and Lovering, 1979[8]	181	Spontaneous reports to manufacturer with retrospective follow-up by mail	19 (10%)	6 (3%)
Sutherland, 1992[15]	86	Spontaneous reports to the manufacturer	4 (5%)	0 (0)
Jamieson and Pearn, 1989[16]	14	Retrospective study of children	3 (21%)	1 (7%)
Tibballs, 1992[6]	12	Retrospective study of children	0 (0)	0 (0)
Barret and Little, 2003[7]	20	Retrospective study	3 (15%)	Not recorded
Williams et al, 2007[9]	136	Retrospective study of rural health centre records	25 [13]† (18%) [10%]	7 (5%)

* This is a subgroup of all patients with reactions. † Only 13 of the 25 cases reported by the authors meet the definition of allergy (Box 1) and include non-specific features such as tachycardia, hypertension, pyrexia and tachypnoea without features typical of allergy. ◆

hypersensitivity reactions. This should be interpreted with caution because our study was not designed to test the effect of premedication. While a recent study from Papua New Guinea suggested that adrenaline premedication was effective, the study was retrospective, did not use a standard definition for allergic reactions and used selective statistical analysis that did not correct for multiple comparisons.[9] Of the 25 cases reported as immediate-type allergic reactions in this study, only 13 met the definition of allergy (Box 1), and urticaria was reported in only six cases. The low rate of immediate-type allergic reactions (13 of 136 or 10%) and the rarity of skin manifestations suggests that the retrospective nature of the study caused cases to be missed, casting further doubt on the validity of its conclusions on premedication.[9]

A limitation of our study was that antivenom infusion rates, which may be an important determinant of whether a reaction occurs, could not be accurately determined. This was in part because of the differing volumes of protein in each type of antivenom. More problematic was the fact that our study reported the total duration of antivenom administration and it was unclear if this duration included stopping and restarting the antivenom infusion or just the initial infusion rate.

In summary, Australian snake venoms are currently being used appropriately and mainly for coagulopathy. Immediate-type hypersensitivity reactions occur in a quarter of patients, and severe hypotensive reactions in 5%. The low incidence of severe reactions, satisfactory response to resuscitation, and lack of an association between discretionary use of premedication and reactions supports the current approach of most clinicians, who do not use premedication routinely.

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