

Sixteen years of severe Tiger snake (*Notechis*) envenoming in Perth, Western Australia

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SUMMARY

We aimed to describe the characteristics, clinical course, management and outcome of patients presenting to Perth teaching hospitals after envenoming by Tiger snakes. We undertook a chart review from six Perth teaching hospitals over a 16 year period from 1990 to 2005. Data were collected by a trained investigator using a preformatted data abstraction tool. We included patients bitten in the appropriate geographical area, with defibrination coagulopathy and positive Venom Detection Kit result for Tiger snake or response to specific antivenom. Of 381 charts reviewed, 23 patients were envenomed by a Tiger snake. The mean age was 36 years, 83% were male and all were bitten on a limb. First aid was applied poorly and all patients were symptomatic on presentation. Six patients developed rhabdomyolysis, one renal failure, four clinical bleeding, three neurotoxicity, one non-fatal respiratory arrest and one fatal cardiac arrest. All patients received antivenom, 13 received adrenaline premedication, with two mild allergic reactions developing in non-premedicated patients. The average dose of antivenom was four ampoules. Mean hospital stay was 2.6 days. This is the largest series of Tiger snake envenoming reported in Australia. Only one patient of 23 (4%) died, despite all patients being significantly envenomed. With rapid antivenom treatment and modern emergency and intensive care management, most patients envenomed by Tiger snakes survive.

Key Words: Tiger snake, snake bite, envenoming

There is little published on Tiger snake (genus *Notechis*) envenoming in Australia; mostly case reports, with 20 cases reported from 1928 to 1991¹. A summary of 10 case reports by Sutherland and Tibballs includes two animal reports. Clinical effects included coagulopathy, neurotoxicity and rhabdomyolysis; four patients died, two before treatment could be given².

Despite the lack of published data, mortality and morbidity after Tiger snake envenoming has fallen with appropriate first-aid pressure immobilisation,

monitoring of the patient and biochemical markers and the use of antivenom.

Throughout Australia, many snakes make up the Tiger snake group, including *N. scutatus* and *N. ater* species; however in Western Australia there is only one representative, *Notechis ater occidentalis* or the Western Tiger snake.

Recent advances in the taxonomy of the genus *Notechis* suggest low levels of genetic divergence across the genus. As body size and pattern do not contribute taxonomic markers in this group, it has been proposed that all Tiger snakes should be considered part of a single widespread but variable species³. The Western Tiger is seventh on the list of the world's most venomous snake using the LD50 in mice as a guide², and in humans the venom causes coagulopathy, neurotoxicity and myolysis.

About 50% of Tiger snake bites result in significant envenoming and prior to antivenom therapy there was a mortality of 45%¹. Commonwealth Serum Laboratories recommends a starting dose of two ampoules of Tiger snake antivenom or four if there is coagulopathy, severe paralysis, multiple bites or if the bite is by one of the larger subspecies of black Tiger snake. Further doses may be needed to reverse the coagulopathy or reduce the severity of myolysis⁴.

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Accepted for publication on February 3, 2009.

We were interested in the clinical features and antivenom use in patients with significant Tiger snake envenoming. The aim of this study was to describe the severity, clinical course, complications and management in a group of patients with definite Tiger snake envenoming with coagulopathy.

MATERIALS AND METHODS

A chart review using a preformatted data abstraction tool was performed on charts from Sir Charles Gairdner, Royal Perth, Fremantle, Joondalup, Princess Margaret and Armadale Hospitals for the years 1990 to 2005. All envenomed patients in Perth are managed in these hospitals. Charts were sourced using International Classification of Diseases 9 and 10 external coding to capture venomous and non-venomous snake bites (E905, W59, X20).

For the purpose of this study, patients were included if (all of):

1. the bite occurred in the appropriate geographical region for Tiger snakes⁵,
2. defibrination coagulopathy occurred (fibrinogen <0.5g/l or unrecordable prothrombin time/international normalised ratio (INR) if the fibrinogen was not measured), and
3. there was a positive Commonwealth Serum Laboratories Venom Detection Kit (VDK) result to Tiger snake or if not, reversal of envenoming with Tiger snake antivenom.

We chose these inclusion criteria so as to be reasonably certain that the series included only Tiger snake bites. Other snakes in Western Australia, such as Death Adders and Black snakes, may cause paralysis and/or rhabdomyolysis, the other features of Tiger snake envenoming, but without defibrination coagulopathy.

Creatine kinase (CK) levels (U/l) potentially indicating rhabdomyolysis were extracted from case records. The authors used a CK level of 1000 U/l (normal 30 to 170 U/l) to indicate rhabdomyolysis.

We also noted the time to return of detectable fibrinogen or normalisation of activated partial thromboplastin time (APTT)/INR on coagulation screening, and the number of ampoules of antivenom administered prior to this.

The data collected with the preformatted data extraction tool included demographic, incident, pre-hospital and hospital data. Accuracy of data was tested by a second abstractor. Four files (17%) were reviewed using the same data extraction tool. Of 232 data items, 220 (95%) were similarly recorded between abstractors.

Univariate statistical analyses were performed using SPSS (Statistical Package for Social Sciences) version 14. Ethics committee approval was waived as the project was registered with each of the participating hospitals as a quality improvement project after correspondence with the ethics committees' chairmen.

RESULTS

Patient demographics, location and timing

Three hundred and eighty-one files of patients with suspected snake bite were reviewed (128 from Royal Perth Hospital, 119 Sir Charles Gairdner Hospital, 23 Princess Margaret Hospital, 89 Fremantle Hospital, 4 Joondalup Hospital and 18 from Armadale Hospital). Of these, 31 cases were identified as having a positive VDK or clinical syndromes consistent with Tiger snake envenoming. Eight cases were excluded for the following reasons. Four patients had a positive VDK but had detectable fibrinogen and all received Tiger snake antivenom. Three patients had evidence of a clinical syndrome compatible with Tiger snake envenoming but a negative VDK, both receiving Tiger snake antivenom and Brown snake antivenom, so it was impossible to be sure which antivenom was responsible for recovery and hence identify which snake envenomed the patient. Similarly, one patient had a negative VDK and mild coagulopathy but detectable fibrinogen, and received both Tiger and Brown snake antivenom. All eight patients may have had Tiger snake envenoming, but we could not be certain.

Twenty-three (6%) patients met inclusion criteria for definite Tiger snake envenoming. Demographics and circumstances of the bite for this group are reported in Table 1.

TABLE 1
Patient demographics and bite circumstances

Mean age	36 y (range 3-74)
Gender	19 (83%) male, 4 (17%) female
Region	14 (61%) Perth metropolitan, 9 (39%) regional/rural
Location	5 (22%) bush/grassland, 4 (17%) own residence
Time of year	20 (87%) September-February
Time of day	18 (78%) daylight, 5 (22%) after dark
Drug influence	1 (4%) alcohol
Activity at time of bite	10 (44%) walking in vicinity
Anatomy of bite site	16 (70%) lower limbs

Initial treatment

Despite attempts to apply pressure immobilisation bandages, they appeared to be applied incorrectly. Seventeen (74%) patients were recorded as having pressure bandages applied prior to arrival at hospital. In 12 of these cases, how the bandages were applied was not specified nor what was used. Three had pressure bandages applied on arrival at the general practitioner or hospital after at least 15 minutes. One was too tight and had to be removed and reapplied. One was removed to take a swab from the bite site. It was reapplied but removed again 20 minutes after the first dose of Tiger snake antivenom.

The limb was immobilised in 12 (52%) cases. Again, it was not clearly documented how the limb was immobilised. One was immobilised only after arriving at hospital and one after walking to get help following the snake bite. Of the five cases in which there was no immobilisation, three reported walking a distance to get help prior to transport to hospital. The mean time from bite to pressure immobilisation was recorded as 13 minutes (range 0 to 45 minutes).

Sixteen patients (70%) were first treated at a secondary hospital prior to being transferred. Twelve (52%) of those patients were treated with antivenom before transfer.

Clinical features

All patients developed symptoms (Table 2). Local pain was a feature for nearly half and a quarter

TABLE 2
Symptoms experienced by envenomed patients (n=23)

Headache	17 (74%)
Nausea/vomiting	17 (74%)
Abdominal pain	11 (48%)
Local pain	10 (43%)
Bleeding	6 (26%)

TABLE 3
Complications and clinical features of envenoming

Neurotoxicity 3 (13%)	ptosis/diplopia 2 (9%), respiratory arrest 1 (4%)
Cardiac arrest 1 (4%)	death
Bleeding 6 (26%)	bite site 4 (17%) epistaxis 1 (4%) haematemesis 1 (4%)
Rhabdomyolysis 6 (26%)	
Renal failure 1 (4%)	

developed bleeding. Serious complications and clinical features of the envenoming are listed in Table 3.

Investigations

Twenty-two (96%) patients returned a positive VDK for Tiger snake from the bite site or urine. The final patient had no VDK performed because he was bitten on Carnac Island where the only snakes are Tiger snakes.

All 23 patients had incoagulable blood on formal blood investigations. Twenty-one (91%) had unrecordable levels of fibrinogen. The other two (9%) had no initial fibrinogen levels tested but had INR >12 and APTT >150. Six (26%) had elevated CK levels (range of 1049 to 104,000 U/l) indicating a degree of rhabdomyolysis. Two of the patients without initial fibrinogen levels had extremely elevated CK levels (51,700 and 104,000 IU). One patient went on to develop renal failure.

Antivenom administration

The mean starting dose of Tiger snake antivenom was 1.3 ampoules. Sixteen patients (70%) received Tiger snake antivenom as the starting antivenom. Four (17%) received a starting dose of Tiger and Brown snake antivenom (mean two ampoules), one (4%) patient received Brown snake antivenom (2.5 ampoules) first and two (9%) patients received polyvalent antivenom first before a positive identification was made for Tiger snake.

Twelve (52%) patients were given premedication of subcutaneous adrenaline prior to antivenom administration and 11 were not premedicated. The premedication group suffered no allergic reactions. Of the non-premedicated group, two (9%) patients developed allergic reactions which were treated with steroids and antihistamines. One patient developed a mild pruritic rash and one developed palpitations which led to transient ventricular tachycardia.

The mean and median dose of Tiger snake antivenom was four ampoules. Fifteen patients received four or less ampoules, three (13%) received five and three patients (13%) six ampoules (Table 4). One received seven and one patient nine ampoules.

Of the six patients who showed clinical signs of bleeding, four received blood products. A combination of fresh frozen plasma and cryoprecipitate were used. No packed cells were administered. Two patients who did not receive blood products had bleeding from the bite site only. A further 10 (43%) patients were administered blood products without clinical bleeding. Time intervals associated with antivenom administration are listed in Table 5.

TABLE 4
Doses of antivenom (ampoules) by number of patients

1 ampoule	2 patients
2 ampoules	3 patients
3 ampoules	4 patients
4 ampoules	6 patients
5 ampoules	3 patients
6 ampoules	3 patients
7 ampoules	1 patient
9 ampoules	1 patient

TABLE 5
Time intervals associated with antivenom administration

	Mean time interval (range)
Bite to first dose of AV	3.2 h (0.1-15)
Bite to detection of fibrinogen	10.8 h (2.8-19.3)
Start of AV to detectable fibrinogen	7.6 h (2-17)
Bite to last dose of AV	8.9 h (1.6-17)
Last dose AV to detectable fibrinogen	3.2 h (0-12)

AV=antivenom.

Mortality

The patient who died was a 15-year-old male. He was catching snakes with his father, a herpetologist. He was bitten at 1730 hours and soon afterwards developed a cardiac arrest, treated with 12 defibrillation attempts on route to hospital. The cardiac arrest may have been a result of the venom load or possibly an allergic reaction to the venom. Cardiac arrest may have been caused by sudden prothrombin activation resulting in multiple emboli causing coronary and respiratory obstruction and ischaemia. A hypotensive episode mediated by bradykinin release may have also contributed. Because the study is retrospective, it is difficult to determine from case notes the true cause of death. He was given three units of polyvalent antivenom on arrival to hospital at 1820 hours. He was coagulopathic on first blood review (INR 3.7, APTT >150) but fibrinogen was detectable. His CK level at this stage was 360 U/l. Two and a half hours later fibrinogen was undetectable and CK had risen to 7160. He developed all the complications of Tiger snake bite envenoming including coagulopathy and rhabdomyolysis, in addition to ischaemic brain injury. Because of the early implementation of life support measures, specific identification of paralysis was not documented. He was given 10 ampoules of antivenom in total, eight units of fresh frozen plasma

and four units of cryoprecipitate. The coagulopathy normalised after six ampoules (three polyvalent and three Tiger snake antivenom) of antivenom, however the CK level rose to 51,700 U/l. He was given a further four ampoules of Tiger snake antivenom due to his continuing deterioration, however he was declared brain dead at 0020 hours the following morning.

The patient who developed a respiratory arrest was a 50-year-old male herpetologist. He was bitten feeding a snake at 1345 hours. He lost consciousness shortly afterwards (Glasgow Coma Score 4/15) and required CPR on route to the hospital. He arrived at the hospital 45 minutes later and was intubated on arrival.

The cause of the loss of consciousness may have been related to the venom itself, as it has the ability to produce paralysis and death in as little as 30 minutes. As in the previous case, a number of causes are possible.

A dose of one ampoule each of Brown and Tiger snake antivenom was given 20 minutes after arriving at hospital. Initial CK was 272 and fibrinogen was unrecordable. A further three doses of Tiger snake antivenom were given over the next hour following a positive urine VDK. He developed coagulopathy and rhabdomyolysis. The fibrinogen level was measurable four hours after the last dose of Tiger snake antivenom, although CK rose to 1110 U/l. Seven units of fresh frozen plasma and 16 units of cryoprecipitate were administered. He showed no clinical signs of bleeding. He made a full recovery and was extubated the following day. The same patient was envenomed by a Tiger snake 17 months later. He developed a coagulopathy and received a further nine ampoules of antivenom. He made a full recovery.

Hospital admission

Twenty (87%) patients were admitted to the intensive care unit. The mean intensive care unit stay was 24 hours (11.2 to 44.5 hours). The other three were managed in the emergency department observation ward. Overall, the mean hospital stay was 2.6 days (0.6 to 25.8 days).

DISCUSSION

This is the largest series of envenoming from Tiger snake bites reported in Australia. Although Tiger snake bite was rare over the 16-year period, with an average of one to two cases per year, this group of 23 patients with significant envenoming had serious morbidity and one patient died. The patient who died had already suffered hypoxic brain injury

before arrival at hospital. We cannot generalise our findings to all Tiger snake bites however, particularly those without coagulopathy, as our inclusion criteria were designed to capture only those with definite significant envenoming.

As in previous studies of snake bite, first-aid rates and effectiveness appeared to be poor⁶ although documentation was not good. All patients developed envenoming despite the attempts at pressure immobilisation, suggesting this was either applied late, incorrectly or was ineffective. As previously suggested⁷, this is an issue that needs to be further researched and training addressed and improved in the community.

Antivenom doses were consistent with recommendations in the literature, with six patients receiving five or six ampoules in total. The dilemma in antivenom dosing is judging the amount of antivenom required to neutralise an unknown venom load, without hard clinical endpoints against which to titrate. Antivenom of course, does not per se cause regeneration of coagulation factors, and there is a delay to normalisation of coagulopathy after adequate antivenom. A large dose of antivenom may be unnecessary and possibly harmful, while it is clearly dangerous to leave venom un-neutralised with the risk of haemorrhage.

The 10 patients who showed no signs of bleeding clinically received blood products prior to the return of fibrinogen and five of these patients received a further amount after fibrinogen was detected. The current recommendation from the antivenom manufacturers suggests the use of fresh frozen plasma and cryoprecipitate should be reserved for patients with active bleeding following complete reversal of all circulating venom with antivenom⁴.

Unfortunately the required dose of antivenom to completely neutralise venom is unknown. The potential problem is that administering fresh frozen plasma prior to the reversal with antivenom may provide more substrate for the prothrombin activator toxin, increasing the production of fibrinogen degradation products, which in themselves are anticoagulant, and theoretically worsen and prolong coagulopathy. Cryoprecipitate, because it contains more fibrinogen, is of even more concern for the same reasons⁸. In our study only six patients had clinical signs of bleeding, yet 13 other patients received blood products. There is no evidence in patients without bleeding that administration of coagulation factors improves or accelerates recovery following the neutralisation of venom with antivenom.

Of the 23 patients, only two (9%) developed mild allergic reactions and needed treatment. Eight patients (34%) were not premedicated but did not show any symptoms of an allergic reaction. This low rate of allergic reactions in non-premedicated patients is in contrast to a recent prospective study⁹ in which 11 (79%) of 14 patients developed systemic hypersensitivity reactions to Tiger snake antivenom. Although this study reflected high rates of hypersensitivity reactions, it was thought to be related to the batch of antivenom, i.e. the possibility of relatively poor antivenom preparations.

This study has several limitations. It is retrospective and relies on sometimes incomplete or inaccurate case notes and involves a small sample size. By studying only patients referred and admitted to Perth teaching hospitals, there may be a referral bias. Inclusion criteria relied on positive VDKs or response to antivenom. VDKs occasionally produce false positive results, although as coagulopathy was another inclusion criterion, these patients must have been envenomed. Equally, there may have been negative VDKs in some patients with envenoming, meaning they were omitted from the series if they did not develop coagulopathy. The restrictive definition of Tiger snake envenoming could have excluded cases presenting late where coagulopathy may have spontaneously resolved, or those cases presenting with only paralysis and/or myotoxicity.

CONCLUSION

Tiger snake envenoming is a potentially lethal condition associated with serious clinical complications and requires urgent treatment. We found four ampoules to be the mean dose of Tiger snake antivenom used to treat envenomed patients in Perth hospitals. We confirm the finding of previous studies¹⁰ that because pressure immobilisation bandages are poorly applied in the community, they may be relatively ineffective. With prompt antivenom treatment and modern emergency and intensive care management, mortality after Tiger snake envenoming is now unusual.

ACKNOWLEDGEMENTS

We thank Associate Professor S. Brown, Associate Professor I. Jacob and Dr J. Yeung, research assistant E. Macdonald and all the staff of the respective hospitals' medical records departments.

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