Lets talk about snakebite management; a discussion on many levels

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Key Findings

1. Clinicians must be mindful of the interplay between coronial and media interpretations of clinical processes and the impact on community trust.
2. Opinion regarding dosing of antivenom continues to be debated amongst experts.

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3. Fatal haemorrhage from snakebite can occur in the presence of adequate antivenom administration.

Abstract

We want to discuss antivenom use in snakebite clinical practice guidelines. Coronial reviews in Victoria of two cases of snakebite envenomation, one described in detail below, prompted us to submit this paper for a wider audience and debate.

Venom and antivenom levels were measured in the case detailed below, but not in the other. The coroner received conflicting and varied advice from experts regarding the dose of antivenom. The Victorian Department of Health and Human Services and the Australasian College for Emergency Medicine (ACEM) were instructed to review snakebite management guidelines, particularly with respect to antivenom dosage.

The discussion that took place amongst medical experts led to considerable media attention. We discuss the potential fallout when there is no consensus amongst medical experts.

Keywords

Snakebite, Snake Venom, Venom, Antivenom, Envenomation, Coagulopathy, coroner, public health, trust, expert opinion

(Word count 315)

The Case

A 70-year-old woman from northwest Melbourne was found at 12:30am by her husband moaning in bed approximately 1.5 hours after retiring. A one metre long snake was on the bedroom floor.

She complained of nausea, pain in her left foot, abdomen and back and the attending paramedics noted faecal incontinence, vomiting and marks on her left foot. A pressure immobilisation bandage was applied from foot to thigh before transport to the ED.

On initial assessment in the ED, about 2 hours post bite, she had normal vital signs (pulse 92bpm, BP 140/70mmHg and oxygen saturation 95% on 2 litres nasal prong O₂) and a slight ptosis. A swab taken from one of her bite wounds (Figure 1 Bite Wounds) was strongly positive for tiger snake using the Snake Venom Detection Kit (SVDK; Seqirus, Parkville, Australia).

After consultation with a toxicologist and confirmation of coagulopathy (INR >8.5 (0.8-1.2), APTT >220 seconds (23-36s), D-dimer >9000 and fibrinogen <0.4g/l (2-5g/l) (Table 1), two vials of tiger snake antivenom (AV) (Seqirus, Parkville, Australia) diluted in sterile saline were administered over 15 minutes at about 3.5 hours post bite. An hour later the patient could not open her eyes, had mild dysarthria and normal limb power. At 7 hours post bite, her ptosis had improved and her vital signs remained stable. A short time later she developed acute hypotension (mean arterial pressure (MAP) falling to 40mmHg). She developed right abdominal pain on deep palpation with no blood loss seen on a rectal examination or via a nasogastric tube. She was initially treated with metaraminol and intravenous fluids. She was too unstable to transport from the ICU for imaging.

At 9 hours post bite her haemoglobin (Hb) had fallen from 131 to 101g/l; she was given ten units of cryoglobulin, six units of Fresh Frozen Plasma (FFP) and a third vial (3000 units) of tiger snake AV (Seqirus, Parkville, Australia). One hour later her BP and Hb again fell; she had more boluses of crystalloid and an adrenaline infusion was started. Further FFP, cryoprecipitate and red cells were transfused for suspected bleeding with persistent severe coagulopathy. Thromboelastometry testing was not available. A bedside transthoracic echocardiogram was normal and her blood film showed no evidence of microangiopathy, severe rhabdomyolysis or significant renal impairment (serum creatinine later peaked at 142 μ mol/L with a creatinine kinase of 1164 IU/L).

At 13.5 hours post bite she developed anuria unresponsive to the administration of 160mg intravenous frusemide, became increasingly hypoxic and developed pulmonary oedema. She was intubated. As she was being prepared for haemodialysis she continued to deteriorate and died 19 hours post bite.

The forensic pathologist reported the cause of death as “tiger snake envenomation”. Post-mortem examination findings included evidence of bleeding into many tissues with significant haemorrhage into the abdomen. (1)

Pre-mortem samples of blood were sent to The Australian Venom Research Unit for Tiger Snake venom and antivenom (TSAV) assays. TSAV was measured using an indirect ELISA method that has been previously described. (2) Tiger snake venom was detected on the initial blood sample at a concentration of 697 ng/ml, which was described as “a level comparable to that found in envenomation of low body weight animals” (1). Six hours following the initial dosing of AV, free tiger snake venom was

not detected and antivenom was detected at a concentration of 1839 mUnits/ml, sufficient to neutralise 18,390 ng/ml of Tiger Snake venom. (3,4) (Table 2)

The Coroner

In reviewing this death and another that occurred in Victoria within 12 months of our case the coroner requested independent expert opinion on the Victorian snake bite management guideline, which recommended the administration of only one vial of AV for confirmed snakebite, (5) a recommendation based upon the 2013 ASP study (6). In the coronal investigation of Mr ST, the second Victorian snakebite death, the coroner was told that the treating intensivist repeatedly questioned the toxicologist's advice not to give more than one vial of AV. (7) The intensivist wrote in his submission to the coroner, that in his opinion, "the guideline for a single dose of AV..failed this gentleman," and asked if a change in practice was needed. The coroner sought three expert opinions to review the management of both cases. (1), (7) In our case, the coroner concluded that following the administration of 2 vials of antivenom initially, there "is no evidence a further antivenom vial...would have altered the outcome." (1) She then directed the experts to specifically consider the one vial recommendation.

One expert maintained that the recommendation for the use of a single vial was evidence based, stating one vial "is sufficient for the vast majority and potentially all cases." (7) A second expert, provided a contrary view, stating the use of a single vial of AV is "clinically unwise..(and).. dangerous." (7) A third expert, suggested that there is a cohort of patients which he termed "outliers," who required more than one vial of AV. (1), (7)

Conflicting advice led the coroner to direct the Victorian Department of Health and Human Services and Safer Care Victoria to review the existing snakebite management guideline and make particular recommendations on the identification and management of "outliers." (1), (7) An expert panel of Australian toxicologists

was convened who recommended no change to the number of vials of AV used in the management of snake bite. They thought that a case definition of “outliers” does not currently exist but may be a focus of future research.

The Media

Media coverage of these two cases raised concerns about whether one dose of AV is enough, reporting “this has been disputed by some experts, who in their evidence to the coroner, said multiple doses could be needed especially in more severe bites.”(8). Australians report high levels of trust in doctors. (9) Establishing trust creates a feedback loop where trust begets better care, which increases trust and satisfaction. (10) Lack of trust in the health system causes disengagement from healthcare and erodes trust more generally. (11) Medical practitioners who treat snake bite patients must understand that patients may know that controversy exists and this may damage the doctor patient relationship.

Clinical Considerations

This cases raise questions regarding the optimal management of snakebite coagulopathy in actively bleeding patients and reinforces some key general lessons. They also demonstrate that massive haemorrhage must always be considered as an ongoing complication for this type of snakebite, irrespective of AV treatment. (12)

VICC occurs in up to 95% of significant tiger snake envenomations in Australia, but major haemorrhage in only 2% (13). Coagulopathic toxins act rapidly, are rapidly eliminated or inactivated with resynthesis of clotting factors and resolution of VCCC occurring within 24-36 hours of snake envenomation (14, 15, 16) regardless of AV administration (14), (17).

Recommendations for treatment of VICC have stated the importance of early and adequate AV administration, but avoidance of coagulation factor replacement except in cases of major or catastrophic bleeding (18), (19) due to the concern that administration of FFP may be ineffective (20) or contribute to further VICC during this period (21). As deficiencies in factors V and VIII are the most significant in VICC, it is also possible that the level of labile factors V and VIII in the administered FFP are of critical importance. (14), (22)

The decision to administer FFP to our patient was based on hypotension, falling Hb and abdominal pain suggesting haemorrhage. A small trial showed that FFP within four hours of envenomation is associated with more rapid restoration of clotting function in snakebite patients (20) and more rapid restoration of clotting factor function. (23) This observation may be species specific. (24), (25)

Our patient received 3 vials of AV that led to successful neutralisation of venom. Three vials exceed the current recommendation. The recent ASP study data showed a significant median decline of AV dose from four vials to one between 2005 and 2015 (13) We have taken the time of envenomation as the time the patient first alerted her husband. If this is the case, our patient received AV within four hours, which is faster than the median time of 4.3 hours reported in the most recent ASP study and which the coroner's experts agreed was "within a reasonable time frame." (1), (13)

Conclusion

Death from snake bite is uncommon in Australia. (26) We recount the unfortunate death of 70-year-old female 19 hours post envenomation by a mainland tiger snake (*Notechis scutatus*) despite the administration of doses of AV that exceed current

Victorian recommendations. Although this patient demonstrated the most common pattern for tiger snake envenomation (venom induced consumptive coagulopathy (VICC) together with neurotoxicity and acute kidney injury) her course was complicated by major haemorrhage. While we believe the number of AV vials was sufficient in our case (based upon our venom/antivenom study results) we agree that the number of vials needed to treat severe envenomation of “outliers” remains unclear and the management of coagulopathy and haemorrhage due to envenomation remains controversial.

Our case further illustrates the unique interplay between research, clinical practice, coronial processes and the resultant media interpretation. It demonstrates the challenging situation that occurs when an unexpected death is unexplainable and how, as clinicians, we must be mindful that we have a duty to communicate what we do not know, as well as what we do.

In her conclusion, the coroner recommended that the clinical details of this case be published in the medical literature so that clinicians are aware of the details. Further, she recommended that the Australasian College for Emergency Medicine (ACEM) circulate her finding to ACEM Fellows to “highlight the evidence, guidelines and potential issues in the management of snakebite.” (1)

As a first line profession, public trust of emergency medicine must be high. The management decisions made in our departments must be evidence based, ethical and transparent. When offering a treatment emergency physicians must communicate clearly and involve patients in management decisions based upon what we don't know as well as what we know.

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Figure 1 Bite Wounds

Figure 2 Selected haematological and biochemical pathology results as well as blood product usage type and timing. (RC – Red Blood Cell units, FFP - Fresh Frozen Plasma units, Plt – Platelet units, Cryo – Cryoglobulin units)

Table 1

Venom and antivenom concentrations and timing - measured by venom specific antigen and antibody Enzyme Linked Immunosorbent Assay (ELISA).

Collection Time	Tiger Snake Venom Concentration (ng/ml)	CSL Tiger Snake Antivenom Concentration (mUnits/ml)
02.54	697	Not detected
06.40	Not detected	1839
12.06	Not detected	1745
12.44	Not detected	1111
14.24	Not detected	878
18.10	Not detected	318

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