Elapid snake envenomation in dogs in New South Wales: a review

J HELLER, DJ MELLOR, JL HODGSON, SWJ REID, DR HODGSON and KL BOSWARD

Elapid snake envenomation in dogs is a commonly occurring yet poorly described clinical entity. Twelve species of dangerously venomous elapid snakes are found in New South Wales that are capable of causing disease in dogs. Geographical distribution of these species varies, as does their venom composition and systemic envenomation syndromes produced in target species. Elapid venom may be divided into the components of prothrombin activating enzymes, lipases and peptidic neurotoxins. Each species of elapid snake may possess venom components that fit any or all of these classifications. The action of these venom components may result in neurotoxic (pre-synaptic and post-synaptic), haemotoxic (red-cell destruction and coagulation disturbance), cardiovascular, myotoxic and secondary nephrotoxic effects. Marked variability may occur in venom composition between and within snake species, resulting in varying toxicity between species and also potentially unreliable clinical syndromes following envenomation. The existence of certain components consistently within the venom of each snake species allows the broad definition of basic pathological processes and clinicopathological changes resulting from snake species-specific envenomation and these are discussed. Diagnosis of snake envenomation is unreliable if based on clinical signs alone and the use of these signs in conjunction with history, physical examination and laboratory investigation, including snake venom detection kits, is recommended. Treatment of systemic envenomation should be undertaken with initial effective first aid and subsequent administration of snake species-specific antivenom.

Key words: elapid snake envenomation, poisoning, dogs


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<th>PT</th>
<th>Prothrombin time</th>
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<td>RBBS</td>
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Elapid snake envenomation in the dog is a poorly described clinical entity. Sparse information exists on disease processes in dogs resulting from envenomation by elapid snakes and there is no current overview available on this topic. Australia hosts around 140 different species of snakes. At least 81 of these species are venomous, and more than 20 are classed as dangerous to humans and animals. Although Australian terrestrial snakes may belong to any of the four families of blind snakes (Typhlopidae), pythons (Pythonidae), colubrids (Colubridae) and elapids (Elapidae), all of the venomous snakes except one (the Brown Tree Snake, Boiga irregularis, a colubrid) belong within the family Elapidae. All members of the elapid family are considered to be venomous, that is, they produce and expel venom. A smaller proportion of these snakes posses the potential to inflict harm via potentially lethal or severe bites. Within NSW, 35 species of elapid snakes may be found and at least 12 of these, belonging to seven genera (Table 1), can be classed as dangerously venomous to humans and animals.

Biological and anatomical features of Australian elapid snakes

Australian elapid snakes are front-fanged (proteroglyphous) carnivorous snakes. Tilting of the fangs to an angle between 10 and 50 degrees from the resting position is achieved by extension of the hinged maxilla to which the fangs are attached. This, coupled with caudal sloping dentition and an ability to disarticulate the jaw, allows envenomation and ingestion of prey much larger than the snake itself.

Venom glands are of modified parotid type, are histologically exocrine in nature and are positioned bilaterally in the posterior part of the head. The glandular material is covered by a fibrous capsule which is anatomically associated with the superior and inferior adductor superficialis muscles, used to consciously regulate the amount of venom that is released during a bite. The venom that is produced here is expelled into venom ducts that run rostrally, through an accessory mucous gland and towards the base of the fangs, where predominantly enclosed grooves facilitate venom transport from base to tip and subsequent injection into the victim.

Geographical distribution of snake species

An understanding of the distribution of potentially dangerous snake species is imperative to limit the number of possible

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species suspected in an incidence of envenomation. A thorough nationwide descriptive distribution is detailed by Shea and accurate pictorial information can also be found in field guides that focus on distributions at a state level.

Identification of snakes
Identification of snakes by lay people and health professionals, has been shown to be highly inaccurate. In a study undertaken by Morrison and colleagues an average of only 19% of people, across all age groups and demographics, managed to identify 10 important venomous Australian snakes correctly. It is thought that this misidentification is due to a combination of factors, including misleading and inconsistent common nomenclature and variation of appearance of snakes within species. The most reliable method of identification of snake species is through assessment of scalation, although unless undertaken by an expert herpetologist, this assessment requires the snake to be dead at the time of examination. A reliable key to the identification of Australian elapid snake species has been presented by Cogger using a combination of detailed appearance and scalation for classification.

Snake venom
The major roles of snake venom are to incapacitate prey, facilitate digestion and to deter predators. Snake venom is composed of hundreds of enzymes, proteins and peptides that act in a diverse manner on numerous molecular targets. The different components of Australian elapid venom can be described as prothrombin activating enzymes, lipases and peptidic neurotoxins. Each species of elapid snake may possess venom components that fit into any or all of these classifications. In addition to these features, Australian elapid venom may be classified as either pro-coagulant or non pro-coagulant in nature.

Prothrombin activating enzymes are present in the venom of many species of Australian elapid snakes in the form of factor Xa-like enzymes that function to catalyse the formation of thrombin, resulting in a disturbance of the coagulation cascade. These prothrombin activators can be divided into four groups (I to IV), of which groups II and III may be possessed by Australian elapids. Both groups II and III function to cleave the peptide bonds in prothrombin, essential for conversion of prothrombin to thrombin. These groups both require the presence of calcium and phospholipid as cofactors, while group II also requires the presence of coagulation factor Va. The consequence of this pro-coagulant action is the stimulation of a disseminated coagulation complex, resulting in grossly abnormal coagulation times, reduced fibrinogen concentrations and massive increases of fibrin and fibrin degradation products.

The major of the numerous lipases found in Australian elapid venoms are phospholipases and in particular phospholipases A₂ (PLA₂). The PLA₂ found in elapid venom may be classified into five types, haemotoxic, myotoxic, neurotoxic, non-toxic enzymatically active and non-toxic enzymatically inactive. These enzymes may result in abnormalities in the coagulation cascade, muscle damage and necrosis, and pre-synaptic neuromuscular blockade. Other lipases such as lysophospholipases, and phospholipases A, B, C and D also exist in some elapid venoms and cause haemolysis and myolysis.

Pepcidic neurotoxins may exist as either long or short-chain molecules and act post-synaptically by binding to skeletal muscle nicotinic acetylcholine (ACh) receptors to block neuromuscular transmission.

Action of venom
The neurotoxic components of elapid snake venom may act either pre- or post-synaptically at the neuromuscular junction to disrupt nervous function. Pre-synaptic neurotoxins take the form of phospholipases A₂ and act by binding selectively and irreversibly to specific sites within the membrane of the nerve ending, blocking neurotransmitter (ACh) release. Pre-synaptic neurotoxins have been shown to bind quickly, but require a latent period of 2 to 3 h to exert full neuromuscular blockade. This latent period decreases with increased nervous activity. Post-synaptic peptidic neurotoxins are less potent than pre-synaptic neurotoxins and are reversible with the administration of antivenom.

The haemotoxic effects of snake venoms include disruption to normal coagulation and destruction of circulating red cells. Prothrombin activators from the venoms of both the Eastern Brown Snake and the Tiger Snake have been isolated and described as Xa-like enzymes that function to catalyse the formation of thrombin, resulting in a disturbance of the coagulation cascade. These activators are responsible for stimulating a defibrination process, more correctly termed ‘venom-induced activation of the coagulation cascade’ but also acceptably described as ‘disseminated intravascular coagulation’ although thrombocytopenia is not always reported. While most elapid venoms exert a procoagulant effect as described, a small number
of toxins may harbour true anticoagulant activity as well or instead.\textsuperscript{22} The basic mechanism of action of the anticoagulant effect has not been fully elucidated. Further coagulation disturbances may occur through the effect of toxin on platelets.\textsuperscript{22} Thrombocytopenia may be a consequence of the disseminated intravascular coagulation complex through the action of thrombin as a known platelet aggregator.\textsuperscript{22} A direct platelet aggregating effect has also been shown to exist in some species\textsuperscript{22} and is associated directly with the action of PLA\textsubscript{2}.\textsuperscript{22} Only one genus, the Copperhead (\textit{Austrelaps}), has platelet inhibitory actions, again mediated through PLA\textsubscript{2}.\textsuperscript{22}

Haemolysis due to Australian elapid envenomation may be caused by either direct or indirect action on red blood cell membranes, and is mediated by a polypeptidic ‘direct lytic factor’, and/or phospholipase activity respectively.\textsuperscript{22} These factors cause structural damage to the erythrocyte cell membrane and result in an influx of water, leading to erythrocyte swelling, stretching and, ultimately, haemolysis.\textsuperscript{22} The presence and severity of haemolysis with respect to different snake and target species is often reported in an ambiguous manner, with conflicting information obtained from various clinical studies.\textsuperscript{22,24,25} Sutherland and colleagues\textsuperscript{25} reported that, despite a range of in vitro effects, there was no evidence of clinical haemolysis for a variety of Australian snake venoms when administered to Rhesus monkeys. However, the results of this study were only obtained for the first 3 h after subcutaneous venom administration, and as such, a slower onset of haemolytic action in vivo may have been overlooked. Further, it has been shown that the sensitivity of erythrocytes to venom-induced haemolysis varies in a target species dependent manner, with dog erythrocytes markedly more sensitive to haemolytic actions than other species such as the cat and human.\textsuperscript{24}

In vitro haemolytic activity is greatest in human red cells for the Black Snake genus (\textit{Pseudochis}) and the Copperhead genus (\textit{Austrelaps}).\textsuperscript{27} although there have been limited clinical studies into the in vivo effects of the toxins from these species in dogs. Early experimental studies undertaken in the 19th century noted that dogs were very sensitive to the haemolytic effect of Red-bellied Black Snake (RBBS) venom both in vitro and in vivo, with a reduction of circulating red blood cells and haemoglobinuria occurring over 24 to 36 h after subcutaneous venom injection.\textsuperscript{28} In the same series of studies, other target species experienced haemolysis after injection with RBBS venom, but only at higher venom doses.\textsuperscript{28} One recent case report has also described a marked intravascular haemolytic response in a dog with RBBS envenomation.\textsuperscript{29} Studies undertaken into the in vivo effects of Brown Snake venom in dogs have made no mention of the presence of haemolysis,\textsuperscript{30} although suggestive signs have been reported in cases of Tiger Snake envenomation in dogs.\textsuperscript{30} The lack of a definitive index for haemolysis, and other possible explanations for the observations noted, such as fluid shifts and concurrent myolysis, reduce the strength of these findings.\textsuperscript{22} It is often asserted that haemolysis and resultant haemoglobinuria from elapid snake envenomation is unlikely to be severe enough to result in significant anaemia or renal dysfunction,\textsuperscript{2,24,25} although this assertion has recently been challenged with the publication of a case report describing severe haemolysis resulting in marked anaemia and fulminant anuric renal failure.\textsuperscript{31} Further study is required in this area given these findings, coupled with a lack of adequate information regarding the effects of certain venoms (in particular RBBS) in dogs. Both leucopoenia and leucocytosis have also been reported as a result of snake envenomation.\textsuperscript{2,24} Leucopoenia occurs in acute envenomation syndromes and appears to largely correct over 30 to 40 minutes.\textsuperscript{22} This acute reduction in white cells is postulated to be the result of entrapment in thrombus formation and is directly related to the prothrombin activator component of venom.\textsuperscript{22} It is likely that the variation in leucocyte count is time-dependent, with acute leucocytopenia developing into a chronic leucocytosis, which has also been reported in a number of studies.\textsuperscript{23,25,32}

It has long been known that some Australian elapid venoms, particularly Tiger Snake and Eastern Brown Snake, may induce profound cardiovascular effects.\textsuperscript{23,33} An initial, sudden fall in systemic arterial blood pressure, with concurrent decrease in cardiac output and stroke volume and increase in pulmonary arterial pressure, may occur following intravenous envenomation.\textsuperscript{23,34} The mechanism of action of this blood pressure disturbance has been the subject of much debate. A series of sophisticated studies undertaken by Tibballs\textsuperscript{23,35,36} investigating the action of Tiger and Brown Snake venoms in dogs, revealed prothrombin activation to directly result in acute thrombotic obstruction to the outflow of the right ventricle, leading to cor pulmonale, impedance of left ventricular filling and resulting in sudden systemic hypotension with concurrent pulmonary hypertension.\textsuperscript{32} Other mechanisms such as direct acting myocardial toxins and the release of vasoactive substances cannot be ruled out.\textsuperscript{23,32}

Myotoxins are defined as venom components that have specific action on skeletal muscle.\textsuperscript{24} The myotoxins found in elapid venoms are in the form of phospholipases and act by causing damage to the integrity of the sarcolemma, resulting in effects ranging from local haemorrhage and necrosis to systemic skeletal rhabdomyolysis producing severe myoglobinuria.\textsuperscript{37} In addition to myoglobinuria, rhabdomyolysis may be responsible for the release of intracellular muscle constituents into the circulation, resulting in myoglobinemia, hyperphosphatemia, hyperkalaemia, metabolic acidosis and intravascular volume depletion.\textsuperscript{38} As with haemoglobinuria, severe myoglobinuria and other sequelae of rhabdomyolysis may result in renal dysfunction, and specifically, acute renal tubular necrosis.\textsuperscript{39,40} Myotoxic effects may also vary in severity depending on the type of muscle targeted.\textsuperscript{41} Muscles containing predominantly fast, glycolytic fibres display greater myolytic sensitivity than those with slow, oxidative fibres.\textsuperscript{42} The mechanism for this difference has not been fully elucidated, but may be due to specificity of the myotoxic components within venom, or to a facilitating effect within certain muscle groups themselves.\textsuperscript{42} Australian elapid venoms, unlike those of other snakes, have not been shown to have direct nephrotoxic effects.\textsuperscript{43} Acute renal failure may result from envenomation due to the indirect effects of...
Tiger Snake (P. textilis)
Eastern Brown Snake (P. textilis)
Tiger Snake (N. scutatus)
Mulga Snake (P. australis)
Red-bellied Black Snake (P. porphyriacus)

Venom variably

Venom composition may demonstrate a large amount of variability. Variation in snake venom may occur, in the most obvious case, between species, but also to a marked extent within species and between individuals. This variability may depend on geographical disparity, age and possibly genetic factors. Seasonal variation has also been reported to account for change in venom composition within species, however, as with diet and sex, numerous strictly controlled studies have failed to confirm an association. The amount of venom injected may also vary greatly and may be regulated by each snake individually. It is thought that the amount of venom produced and expelled is dependent upon factors such as species of snake, geographic origin, sex, body size, time of year and the number in bite sequence.

Venom toxicity

The relative danger of each snake species is dependent on many factors including amount of venom injected into the prey, the ‘efficiency’ of the bite (referring to the ratio of injected to skin-split venom), temperament of the snake, geographical distribution of the snake, number of bites in sequence, age of the snake and relative toxicity of the venom. Although many of these factors are highly variable, the most comprehensive comparison can be obtained from information regarding lethality in mice and average venom yield per bite. Lethality in mice (expressed as median lethal dose, or LD₅₀) is used as a direct measure of the net pathological effect of the overall toxicity of venom. It is an important measure, because the marked variation in venom components and resultant clinical signs render comparison on a clinical level particularly difficult.

Combining the LD₅₀ with average and maximum venom yields from each species allows a more generalised comparison of the danger of each species with each bite inflicted. The comparative lethalities of five snakes found in New South Wales are displayed in Table 2. This table shows that the Eastern Brown Snake has the highest comparative lethality of these five snakes, although all snakes documented are capable of producing many times the lethal dose in mice from one sample alone.

### Table 2. Comparative lethalities of five snakes found in New South Wales.

<table>
<thead>
<tr>
<th>Species</th>
<th>Venom yield (mg)</th>
<th>LD₅₀ (mg/kg for 18–21g mice)</th>
<th>Equivalent number of mouse LD₅₀ doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inland Taipan (O. microlepidotus)</td>
<td>44</td>
<td>0.010</td>
<td>217,820</td>
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<tr>
<td>Eastern Brown Snake (P. textilis)</td>
<td>2</td>
<td>0.041</td>
<td>2469</td>
</tr>
<tr>
<td>Tiger Snake (N. scutatus)</td>
<td>35</td>
<td>0.118</td>
<td>14,893</td>
</tr>
<tr>
<td>Mulga Snake (P. australis)</td>
<td>180</td>
<td>1.910</td>
<td>4709</td>
</tr>
<tr>
<td>Red-bellied Black Snake (P. porphyriacus)</td>
<td>37</td>
<td>2.530</td>
<td>731</td>
</tr>
</tbody>
</table>

* Bovine serum albumin in saline.
† Most venomous snake species in Australia.
found along the eastern coast and ranges of NSW and also in the south of the state. Human bites are rarely reported other than in herpetologists, but these snakes are often found near water and are known to travel long distances during mating seasons, and are therefore accessible to inquisitive domestic species. RBB venom has been described as strongly haemolytic and feebly neurotoxic. The components of RBB venom include Pseudexin, a PLA$_2$ enzyme with pre-synaptic neurotoxicity, indirect and direct haemolytic activity, a myotoxic and haemolytic PLA$_2$, haemolytic PLB$_2$ and a factor X$_a$-like prothrombin activator.

Envenomation by the RBB results in a mild clinical syndrome in adult humans, characterised by necrosis around the area of envenomation, pigmentation, serum creatine kinase (CK) activity elevations, and systemic signs including sweating, nausea and headache. Envenomation by this species in adult humans does not appear to cause paralysis, coagulopathy or significant systemic myolysis, and as such, treatment with antivenom is not required. The clinical syndrome in children may result in more significant clinical signs. Current knowledge regarding the effect of envenomation by the RBB in domestic animals is very limited and, to the authors’ knowledge, only one report of envenomation of a dog by the RBB has been published since 1958. Although literature prior to this date focuses on a reportedly marked haemolytic action in dogs, publications since this time appear to rely on extrapolation from human case reports and experimental envenomation in monkeys, where significant haemolysis or rhabdomyolysis is not described. Given the recent publication of a case report where marked haemolysis and rhabdomyolysis occurred, and in light of the knowledge that considerable differences in the action of snake venoms on erythrocytes and other cell membranes may occur between target species, extrapolation of this nature must be interpreted with caution.

RBB venom can be neutralised with Black Snake antivenom, although Tiger Snake antivenom is also effective and is the treatment of choice due to the lower cost and reduced mass of equine protein per vial.

**Eastern or Common Brown Snake (Pseudonaja textilis)**

The Eastern Brown Snake species occupies all areas within NSW and is usually found in dry country. These snakes are aggressive when provoked and may strike rapidly over short distances, although only 15% of strikes result in envenomation of the target animal. Eastern Brown Snake venom consists of a potent pre-synaptic PLA$_2$, neurotoxin, ‘textilotoxin’, two post-synaptic peptidic neurotoxins, ‘pseudonajatoxin’ a and b and two potent factor X$_a$-like prothrombin activators.

The clinical signs resulting from envenomation by this species are, as with other species, dependent on route of venom administration, although rapid onset of clinical disease often occurs and a severe lower motor neuron paralytic neurological syndrome coupled with a hypocoagulable state predominates. Initial haemodynamic collapse, severe systemic hypotension and thrombocytopenia have also been described and are suggested to be associated with thrombosis and pulmonary outflow obstruction. The clinical syndrome associated with envenomation by this snake species appears to be similar in humans and dogs.

Brown Snake antivenom is effective in neutralising the venom from this species.

**Tiger Snake (Notechis scutatus)**

The Tiger Snake has a wide distribution within eastern and south-eastern areas of NSW and is usually found in regions associated with swamps, rivers and creeks. Tiger Snake venom has been researched extensively and is composed of numerous toxins, of which notexin is the most important, taking the form of a potent myotoxic and pre-synaptic PLA$_2$. Notexin causes marked local and generalised skeletal muscle myodegeneration in a dose-dependent manner, with dogs particularly sensitive to its effects. Notexin also acts presynaptically to reduce the amount of ACh available intracellulary through mobilisation of vesicular ACh, rather than blocking its release directly, resulting in significant neuromuscular paralytic effects.

Numerous other less potent pre-synaptic neurotoxic PLA$_2$ enzymes are also found in Tiger Snake venom and act to block ACh release in a more direct manner. Small amounts of several reversible post-synaptic neurotoxins are also found in Tiger Snake venom, as is a potent factor X$_a$-like prothrombin activator. The presence of a mild haemolytic component to this venom has been suggested, but the results of these studies are not without question.

Envenomation of dogs by the Tiger Snake results in a primarily neurological, myolytic and coagulopathic clinical syndrome. This snake has been described as producing three categories of signs in the dog, defined as pre-paralytic, paralytic and lethal, and sublethal or delayed signs. These categories encompass collapse due to systemic hypotension, vomition, salivation, defaecation, trembling and tachypnoea in the pre-paralytic stage, skeletal muscle paralysis, coagulopathic signs and oliguria with or without haemoglobinuria or myoglobinuria in the paralytic stage and mydriasis, slow or absent pupillary light reflex, stiffness or ataxia, inability to close the jaws and signs of renal failure in the sublethal stage.

The pre-paralytic stage is noted by the occurrence of an initial haemodynamic collapse as discussed for Brown Snake envenomation. The mechanism behind this initial collapse and systemic hypotension has been elucidated by echocardiographic documentation of thrombus formation and subsequent obstruction of the pulmonary outflow tract after administration of a purified Tiger Snake prothrombin activator to the dog. Systemic hypotension, pulmonary hypertension and likely myocardial ischaemia are thought to be mediated through this mechanism.
Delayed presentation after Tiger Snake envenomation has been associated with a reduction in prognosis in humans and dogs.\textsuperscript{65,66} Tiger Snake venom is neutralised with Tiger Snake antivenom.\textsuperscript{63} Mulga or King Brown Snake (Pseudechis australis) Despite the common name of ‘King Brown’, this snake is actually a member of the Black Snake genus and is an example of the confusion that a common name may present.\textsuperscript{7} The Mulga Snake is found in the inland regions of NSW and may grow to a length of up to three meters.\textsuperscript{2} This species of snake is capable of delivering large quantities of venom, although its lethality is noted to be considerably lower than other dangerous elapids.\textsuperscript{14} The venom of the Mulga Snake is primarily myolytic, with the major component identified as ‘Mulgatoxin’, a lethal PLA\textsubscript{2} myotoxin shown to cause marked rhabdomyolysis in mice and monkeys.\textsuperscript{25,69} Neurological abnormalities may occur secondary to morphological damage to muscle fibres, and post-synaptic short-chain neurotoxins have also been recognised within the venom.\textsuperscript{25} To the authors’ knowledge there are no reports of Mulga Snake envenomation of dogs in the literature.

Neutralisation of Mulga Snake venom is with Black Snake antivenom.\textsuperscript{63} Highland Copperhead (Austrelaps ramsayi) The Highland Copperhead is found in south-eastern and northern regions of NSW.\textsuperscript{9} Although the Copperhead can be divided into three species, Lowland Copperhead (\textit{A. superbus}), Highland Copperhead and Pigmy Copperhead (\textit{A. labialis}), with only the Highland Copperhead occurring in NSW, these species have historically been considered as one, previously known as \textit{Denisonia superba}, and often referred to as Australian Copperhead.\textsuperscript{5} Although the venom of the Highland Copperhead has been poorly elucidated, components of the venom of the Copperhead, when it was regarded as a single species only, that have been identified include a PLA\textsubscript{2}, with anticoagulant and antiplatelet activity,\textsuperscript{72} a myotoxic PLA\textsubscript{2},\textsuperscript{69} haemolytic PLB\textsuperscript{51,67} and undefined post-synaptic neurotoxins.\textsuperscript{72} It is unclear which, if any of these components, are found in the venom of the Highland Copperhead.

Copperhead venom (again when regarded as a single species) has been shown to cause considerable rhabdomyolytic effects in mice and monkeys.\textsuperscript{25,69} To the authors’ knowledge, only one case report exists describing the predominantly paralytic effects of envenomation in a dog by these species.\textsuperscript{25} Neutralisation of the venom from this snake species is with Tiger Snake antivenom.\textsuperscript{63} Common Death Adder (Acanthophis antarcticus) The Common Death Adder can be found widely across NSW, however most reports stem from the eastern coast and ranges.\textsuperscript{5} Although this species is known to strike at speed, it is generally a sluggish snake and usually will not strike unless provoked.\textsuperscript{2} The venom is known to contain several short and long chain post-synaptic neurotoxins,\textsuperscript{13} and numerous PLA\textsubscript{2} components.\textsuperscript{14} Death Adder venom is devoid of myotoxic activity,\textsuperscript{25} and although it has been shown to be an incomplete prothrombin activator,\textsuperscript{72} there have been no reports of significant coagulopathic activity either. Case reports of humans reveal neurotoxicity to be the main feature of Death Adder envenomation.\textsuperscript{73} The only case report in a dog identified by the authors lacks definitive diagnosis of snake species but also describes a paralytic syndrome.\textsuperscript{9} Venom neutralisation for this species is with Death Adder antivenom.\textsuperscript{63}
provide greater information about the progression and resolution of myolytic processes.

Although envenomation by Australian elapids may result in renal dysfunction, the use of renal analytes (serum measurement of urea and creatinine) to aid in diagnosis may only be helpful if the presentation is delayed.66 Use of these analytes for monitoring progression of renal function is, however, imperative in cases of snake envenomation where renal compromise has occurred.76

The pathogenesis and progression of each myolytic process may vary between snake species and is dependent on the specific action of each myolytic toxin. Therefore, although an increase in biochemical markers such as CK and AST activities may be indicative of active muscular damage, their use as an indicator for disease progression may be misleading. The use of multiple modalities such as quantitative macroscopic, histological and biochemical information to estimate the extent of the myonecrosis secondary to snake envenomation has been postulated as the most thorough way to characterise this entity.23,25,32 Obvious limitations to this approach include the invasive nature of the procedure, time for accurate histopathological analysis and variation in histological features dependent on time after envenomation.37

Haematological changes may vary with the course of disease. Thrombocytopenia and leucocytopenia may occur early in the disease and are associated with thrombus formation, while a leucocytosis may develop later in the disease process and is indicative of an inflammatory response with a possible stress component.23,25,32 Reports have also detailed persistent thrombocytopenia in cases where complete defibrination is evident.85 Further studies are needed to confirm these haematological changes.

The presence of a coagulopathy, measured by elevation of prothrombin time (PT) and activated partial thromboplastin time (APTT) is used in human medicine as a reliable indicator of snake envenomation, although it is noted that normal coagulation status does not preclude the possibility of envenomation.78 Results of observations of coagulopathic status in dogs and cats revealed similar results in dogs as in humans, although the same tests were poorly predictive of envenomation in cats.86 No studies have quantified the diagnostic value of measurement of coagulopathic status for snake envenomation in any species. Activated coagulation time may also be used as a quick patient-side test to assess the coagulopathic status of a patient. No studies have evaluated the potential use of this measurement for diagnosis of snake envenomation.

Fibrinogen (ogen) Degradation Products (FDPs) occur as the result of fibrinolysis, and are increased as a result of procoagulation.27 In cases of snake envenomation where prothrombin activation results in a coagulopathy (measured by elevations in PT and APTT), secondary activation of the fibrinolytic pathway should result in an increase of circulating FDPs.39 Although detection of elevations in FDPs are discussed in many case reports of snake envenomation in humans and also domestic species,23,32 there have been no controlled studies to assess the efficacy of detection of FDPs for the diagnosis of snake envenomation.

Analysis of the urine may be used to identify the presence of myoglobinuria and/or haemoglobinuria. Methods such as spectrophotometric analysis, electrophoretic separation, high performance liquid chromatography and immunochromatography analysis enable accurate differentiation between haemoglobin and myoglobin pigmentation,96 however, these techniques are often not readily available and differentiation of these two proteins is difficult in a normal laboratory setting, as both give positive results for tests for haeme.99 Clinically, increases in CK and AST activities along with a brown urinary pigment occurs with myoglobinuria, while pink serum with pink or red urinary pigment occurs with haemoglobinuria.99 The presence of both pigments may result in a combination of these changes.

Assessment of urinary pH is helpful for prognosis and treatment of animals with myohaemoglobinuric renal failure because alkaline urine has been found to inhibit the development of renal tubular necrosis secondary to myoglobinuria.100 The solubility of myoglobin decreases with a reduction in pH, and therefore by increasing the pH an increase in solubility can be promoted, resulting in increased renal excretion of the pigment and a reduced likelihood of haeme protein-induced ARF.20 For ongoing assessment of renal function, monitoring of urinary output and the USG of the patient is important, in conjunction with assessment of the renal analytes.76

Snake venom detection kits

The diagnostic tests that have been described above provide information regarding the biochemical and physiological effects of snake envenomation, although none are specific for the entity of snake envenomation itself. Accurate and definitive diagnosis allows the administration of a monovalent antivenom, rather than the large volume of polyvalent antivenom that is necessary for treatment of unknown snake envenomation.20 The use of monovalent antivenom is recommended because it is cheaper and associated with fewer complications.25

The snake venom detection kit (SVDK), a rapid in vitro sandwich enzyme immunoassay, enables detection of venom from the five major genera of snakes within Australia (Tiger, Brown, Black, Death Adder and Taipan).20 This test was developed by the Commonwealth Serum Laboratories (CSL Ltd, Parkville, Australia). It may be used on a swab from the bite site, urine or blood, although the initial two samples are preferred, and utilises a lyophilised rabbit antibody-enzyme conjugate specific for each of the five main snake species.20 The test takes 20 minutes to complete and the result indicates the antivenom needed to neutralise the envenomation syndrome, rather than the species of snake responsible, allowing greater specificity of the test and generalisation for use with envenomation by less common snake species.20

Information on the diagnostic sensitivity and specificity of this kit for snake envenomation has not been published by the manufacturer. The manufacturer states that the primary reasons for this are the difficulties arising from snake venom variation within species and immunoype, however, CSL regards the kit as highly sensitive (Tim Carroll, CSL Ltd, personal communication).
The possibility of cross-reaction of the SVDK with mildly or non-venomous species has been assessed recently by Jelinek and colleagues. This in vitro study found that false positive results may occur in cases of non-medically significant snake envenomation, highlighting the need for restriction of the use of SVDKs to patients who display typical systemic signs, irrespective of whether they have been seen to be bitten by a snake or not. This study also demonstrated that venom from many of the elapids considered mildly venomous was not detected. This finding may have implications for animals suffering envenomation by snake species not considered dangerous for humans, but whose threat is as yet unknown for animals.

**Treatment of snake envenomation**

The use of effective first aid as the first line of treatment for snake envenomation acts to slow the systemic spread of venom from the bitten area and delay the envenomation syndrome. Venom is known to be distributed systemically within the lymphatic system and venom distribution can be impeded by limiting lymphatic movement within the body. The application of a firm crepe bandage, splint and complete immobilisation of the affected limb results in little movement of venom and, as a result, systemic envenomation can be avoided for lengthy periods.

Antivenom is the treatment of choice for systemic elapid snake envenomation. Antivenom is formulated from hyperimmune equine serum (IgG). Administration of antivenom is indicated wherever there is evidence of systemic envenomation and the amount required varies depending on the amount of venom instilled. Each vial of antivenom is sufficient to neutralise the average amount of venom obtained by milking a snake of the same species, although studies have revealed that some cases of envenomation, particularly by Tiger and Brown Snake species, may require substantially more than the recommended dosage.

The antivenom currently available in Australia is categorised under seven different formulations: Brown Snake, Tiger Snake, Brown and Tiger combined, Black Snake, Death Adder, Taipan and Polyvalent antivenoms. Use of polyvalent antivenom is not recommended due to its relatively high cost, the large volume required and the increased risk of adverse reaction. It is recommended that the antivenom is diluted 1 in 10 with a polyionic intravenous fluid and instilled intravenously over 15 to 30 minutes whilst monitoring for adverse reactions.

**Adverse reactions to antivenom**

Adverse reactions can be divided into acute and delayed forms. Acute adverse reactions occur in the form of anaphylactic/anaphylactoid reaction (grouped as anaphylaxis) to the administration of a foreign protein. Histamine and a variety of other inflammatory mediators are released, causing bronchospasm, hypotension and oedema of the airways and lungs, resulting in a life-threatening clinical scenario. Delayed adverse reactions, in the form of serum sickness, a type III hypersensitivity, have also been reported in humans up to 2 weeks after the administration of antivenom. Usually responsive to glucocorticosteroid therapy, serum sickness presents with varying severity and may involve pyrexia, lymphadenopathy, urticaria and polyarthropathy. To the authors’ knowledge, there are no published reports of anaphylaxis in dogs due to elapid snake antivenom administration, or serum sickness. However both effects are documented in humans. The rate of adverse reactions in humans to Australian snake antivenoms are reported to be considerably lower than to foreign snake antivenoms, with a recent Australian estimate of 4.6% of cases when premedication is used.

There is considerable debate within the literature over the use of premedicants to reduce the incidence of anaphylaxis secondary to snake antivenom administration. Adrenaline is the drug of choice for treatment of anaphylaxis, although rapid or large dose administration of this drug is associated with hypertension. In the coagulopathic patient, hypertension may increase the risk of severe haemorrhage and a number of snake bite deaths secondary to cerebral haemorrhage have been reported in humans. Although there are no substantial data to support or repudiate the association of the use of adrenaline with these deaths, current recommendations regarding the use of adrenaline as a premedicant suggest low doses by the subcutaneous or intramuscular route. The use of an antihistamine premedicant, and in particular H1-receptor blockers, may be helpful to antagonise the effects of histamine, a likely cause of some adverse reactions. The use of corticosteroids in conjunction with antihistamines has been shown to reduce anaphylaxis to antivenoms for Sri Lankan snakes and also to other foreign proteins, including radiographic contrast media. The applicability of these strategies to Australian antivenoms is currently unknown.

Intravenous fluid therapy is required to support the patient, reverse hypovolaemic shock and decreased cardiac output, and to maintain urinary output. The type of fluid administered should be dependent on the clinical scenario, assessment of acid-base status, degree of hypovolaemia and presence or absence of haemolysis or coagulopathy. Blood products including whole blood, packed red cells and fresh-frozen plasma may also be required in cases of uncontrolled bleeding due to coagulopathy or significant haemolytic anaemia and following neutralisation of all circulating venom with appropriate antivenom therapy.

The role of corticosteroids in treating serum sickness and possibly for the reduction of anaphylaxis has been discussed. However, steroid therapy may also have a role in blocking the effects of PLA2. Further studies are required before firm recommendations can be made. Patients with significant rhabdomyolysis may benefit from pain relief, along with volume expansion, administration of mannitol and urinary alkalinisation to protect against acute tubular necrosis. One study has shown the use of pentoxifylline, a methylxanthine, to be nephroprotective in rats with myoglobinuric...
acute renal failure, although this drug has not been tested in other species as yet.77

The use of Vitamin C for the treatment of snake envenomation has been reported in non-peer reviewed publications, however the reported benefits are anecdotal and there is no evidence to support its use in the scientific literature. Furthermore, the use of large doses of vitamin C may result in urinary acidification, which is contraindicated in cases where rhabdomyolysis and pigmentation is evident.76,78

Heparin has been shown to be effective in reducing the defibrillation syndrome resulting from prothrombin activation if it is administered prior to the envenomation process.79 However, it is ineffective, and may even potentiate the resulting coagulopathy, if administered after envenomation has occurred and as such, heparin is not recommended for treatment of established snake envenomation.82,83

Conclusions

This paper has presented a review of Australian elapid snake envenomation in the dog, with particular reference to snake species that are common in NSW. Although information on elapid snake envenomation in dogs is sparse, a broad knowledge exists of the basic physiological processes and clinicopathological findings resulting from envenomation by individual snake species and these have been discussed. Further research in this area is required to define these clinical syndromes and resulting physiological and clinicopathological changes accurately in the dog, particularly with respect to species other than Tiger Snakes and Eastern Brown Snakes that are considered of lesser importance to humans.

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