

SNAKE ENVENOMATION OF COMPANION ANIMALS

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Introduction

The notes represent a summary of some the literature since 2000 on Australian snake envenomation. There are fascinating new developments in the treatment of snake envenomation. The conclusions from the literature and our own clinical practice remain largely consistent with those of the review and clinic observations I wrote for the University of Sydney Post Graduate Committee in Veterinary Science Toxicology course held in 1999 ("Snake Envenomation of Companion Animals"). This old review is attached.

Summary

- Most deaths are the result of delayed, inadequate or inappropriate administration of antivenom (Struan Sutherland 1980)
- Most people and many physicians cannot correctly identify snake species.
- Preparalytic signs = potentially lethal envenomation
- Be prepared for rapid deterioration
- Treatment often requires multiple doses antivenom especially for Brown, tiger, taipan and Mulga snake (king brown) envenomation. Severe envenomation always requires multiple antivenom vials.
- Early treatment results in an easier to reverse neuromuscular blockade
- Early treatment after pre-paralytic signs but before onset of serious envenomation may greatly decrease the dose of antivenom required.
- Mechanical Ventilation saves lives. The old green Bird ventilators are still available and are relatively easy to use (from AAS cost approximately \$1000)
- CSL venom detection kit has a low sensitivity. The CSL Venom detection kit is not an accurate predictor of definite envenomation. False positives are possible especially following bites with some the lesser venomous elapids and even some pythons, the test will sometimes show positive for tiger snake. On the other hand no false positives (100% specificity) were detected on the examination of the urine from 50 dogs and 25 feline non-envenomated patients.
- Samples for the CSL Venom detection kit in order of preference are: bite site, urine, blood.
- Long latency periods in cats and on occasion, dogs up to 25 hours until onset of clinical signs, often severe, have occurred in our own practice, where animals have been caged overnight. (= must observe suspect patients for 25hrs).

There is a 2003 report of a severe fulminating tiger snake envenomation in a young woman that took 32 hours to appear after the bite.
- Successful resuscitation after cardiac arrest is possible in man, dogs and cats if prompt CPR and IV antivenom
- Monovalent antivenoms from CSL often do possess activity against other snake venoms, but

concentrations and affinity of antibodies for other species of snake venom are variable and as such antivenom cannot be used reliably in the clinical setting for snake species other than the intended. The exception is in the case of black snake envenomation where tiger snake antivenom is appropriate, but mulga snake (a member of the black snake family) envenomation requires treatment with black snake antivenom. The mulga snake produces large amounts of venom and often inflicts multiple strikes.

- There is some cross reactivity in the neutralizing ability of antivenoms against procoagulant activators but not consistently with neurotoxins
- Each species of the 6 most venomous snakes produces a characteristic and specific envenomation syndrome in each of the domestic animal species and man but correlations between securely identified species and the domestic animal envenomation syndromes have been slow to develop.

Variations between domestic animal species

- Paralysis because of neuromuscular blockade (or myotoxin induced paralysis in the case of the mulga snake) occurs with all 6 dangerous elapid species
- Coagulopathy (brown, taipan, tiger, mulga snake in dogs)
- Rhabdomyolysis, myoglobinuria & renal failure (sea snake, mulga, tiger & taipan)
- Renal toxicity (Tiger and black snake spp)
- Haemolytic venoms (all black snakes but especially red-bellied and copperhead)
- Limb or facial swelling (black snake species)

However it must be stressed that diagnosis based on clinical signs alone remains unreliable. The use of clinical signs combined with local geographic knowledge of the distribution of snakes, history and laboratory investigations including the use of snake venom detection kits or the accurate species identification of the offending snake is recommended

- Most of the signs of envenomation are due to the neurotoxins (or myotoxins) and the prothrombin activator & venom induced consumptive coagulopathy (VICC).
- In human envenomated patients that develop VICC there is a depletion of fibrinogen, factor V and factor VIII with an INR (prothrombin time index) and an aPTT that exceeded upper limits of detection yet Prothrombin levels never fell below 60% of normal suggesting that the procoagulant toxins were rapid in onset and rapidly eliminated and resynthesis of clotting factors occurred irrespective of antivenom. The clotting abnormalities are faster with brown snake than tiger snake. Resolution of VICC occurred within 24-36 hours irrespective of snake type
- VICC is not a DIC (which is activated by tissue factor/factor VIIc pathway). VICC may be associated with thrombotic microangiopathy (for example renal failure)
- In humans the administration of Fresh Frozen plasma (FFP) decrease the time to recovery from VICC where as antivenom dose and time of antivenom administration had no influence of time to recovery.
- In brown (dugite) snake envenomated dogs treated with antivenom, of 6 administered FFP, 2 died; of the other 6 dogs that received antivenom and saline, all lived. Post mortem of the 2 dead dogs revealed massive intravascular clotting. Also afibrinoginaemia persisted regardless of antivenom dose.
- Old CSL antivenoms do retain considerably activity for years after the stated expiry date. Antivenom that has been frozen and thawed or left at room temperature for 3 days caused only small decreases in activity
- In man hypersensitivity reactions to antivenom are common, but the discretionary use of premedication was not associated with reduction in reactions. More reactions occurred with tiger and polyvalent antivenoms (41%) vs brown snake (10%)
- Brown snake antivenom does not bind well to the low molecular weight protein components of venom

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I. INTRODUCTION

Over the previous 18 years, for 3 different 2-3 year periods, the incidence, diagnostic methods, treatment and outcome of companion animals that have suffered snake envenomation is reviewed. Our practice is situated in north-west N.S.W and the predominant snake envenomations are by brown snake (*Pseudonaja* genus) 72%, followed by king brown (*Pseudechis australis*) 13%, and more infrequently tiger, whip and black snake. The basic tenets of treatment have not changed in 18 years, that is the prompt administration of adequate amount of the appropriate antivenom but there has been considerable refinement in the intensive care of the severely envenomated patient with resultant improvement in outcomes, both with regard to survival and minimising morbidity such as post-envenomation renal failure, pyothorax and myasthenia. Attention is drawn to several factors that have profound clinical implication:

- the frequent need for respiratory support for snake envenomated patients.
- occurrence of pre-paralytic signs as heralding an almost invariable lethal dose of venom unless treated.
- the large variability of the injected dose of venom and the frequent requirement for multiple ampoules of antivenom

- the profound coagulopathy that occurs during envenomation, especially by brown snakes, tiger snakes, taipans and some species of black snakes, due to the high level of procoagulant prothrombin activator in the venom and the poor avidity of CSL antivenom for the prothrombin activator component of venom than for other components such as the neurotoxins.
- The relatively low success rate for correct identification of the offending snake using the CSL venom detection kit and some explanations for this performance including the time course of the concentration of venom found in both blood and urine
- One envenomated cat had a 24.5 hr. latency period between being bitten by a snake and developing signs of envenomation, which required antivenom and ventilatory support.
- The tantalising clinical impression that treatment with the appropriate antivenom in a patient for which the offending snake has been positively identified and in whom only the preparalytic signs of envenomation have occurred requires only a minimal dose of antivenom to prevent progression along the usual course of a severely envenomated patient
- The relatively common occurrence of sublethal envenomation especially in cats, that may not require the administration of antivenom
- there appears to be a direct correlation in the time between clinical envenomation to treatment period and the treatment to recovery period.
- delayed treatment is often associated with hypothermia in envenomated animals

Additionally a brief review of the published literature on Australian snake envenomation over the last 15 years is made

The Incidence of Snake bite in Domestic Animals

Mirtschin et al (1998) ⁴ in a survey of 10% of Veterinarians listed with the AVA (379) and selected at random across Australia, received 106 replies of which 61 reported snake bites, 19 had no snake bites to report and 26 were no longer in practice, makes a rough estimate that there is approximately 6240 snake bite cases that are presented to Veterinary practices each year. The real number is likely to be higher as some animals survive a snake bite unknowing to their owners, others are not presented to Veterinarians, or die before they arrive at a veterinary practice.

Bites were predictably more common in rural areas (78%) compared to urban areas (22%). But interestingly there was an environmental influence with urban areas cats accounted for 66% of the reported snake bites and dogs 34%, whereas in rural areas dogs and cats each accounted for 47% of recorded snake bites. The species of snake responsible for envenomation varied with their geographic distribution.

STATE	Brown	Tiger	Taipan	Black	Unknown	Total
QD	83%	16%	2%	5%	8%	67
NSW	89%	4%	0%	10%	1%	29
SA	96%	0%	0%	0%	6%	32
VC	32%	55%	0%	0%	9%	24
WA	77%	22%	0%	0%	0%	10
TAS	0%	100%	0%	0%	0%	2
ACT	93%	0%	0%	6%	0%	15
NT	100%	0%	0%	0%	0%	1

Mirtschin et al show that the administration of antivenom significantly improves the chance of survival of domestic animals bitten by snakes. Overall 91% of cats and 75% of dogs survived snake bite following the administration of antivenom, whereas of untreated animals 66% of cats and 31% of dogs

survived.

The Incidence of snakebite in patients of South Tamworth Animal Hospital

A retrospective review of cases of snake envenomation seen at South Tamworth Animal Hospital over 3 periods:

24 months from 1/10/80 to 1/10/82²⁰

28 months from 16/12/88 to 2/5/91

36 months from 5/9/95 to 5/9/98

(see appendix 1) is presented below

1) Incidence

PERIOD	cat	dog	horse	Total
1/10/80- 1/10/82	24	12	0	36
16/12/88 2/05/91	39	22	1	62
5/09/95- 5/09/98	45	22	0	67
TOTAL	108	56	1	165
%	65%	34%	1%	100%

2) Snake species responsible for domestic animal envenomations

2 methods were used to identify snakes: morphological examination using Coggers guide to identification²² and the Commonwealth Serum Laboratories ELIZA test "Snake Venom Detection Kit".

PERIOD	MORPHOLOGICAL IDENTIFICATION						COMMONWEALTH SERUM LABORATORIES ELIZA TEST "SNAKE VENOM DETECTION KIT"				POSITIVE IDENTIFICATION NO CASE
	BROWN		BLACKSP		TIGER	VMP	BROWN	BLACKSP	TIGER	NEGATIVE	
	MUGA	REDEIL	BLURRIL								
1/10/80 1/10/82	6	0	0	0	0	0	1	0	1	35	836
16/12/88 2/5/91	6	1	0	0	0	0	4	2	1	10/17	1462
5/9/95 5/9/98	11	3	2	1	0	2	5	0	0	6/11	2167
TOTAL	23	4	3	3	0	2	10	2	2	19/33	4615
%										58%	28%

From the above table it can be seen that the positive identification of the offending snake responsible for envenomation was only determined in 28% of cases. Brown snakes account for 72% (33/46 cases) of the envenomations where the snake species was identified, black (pseudonaja genus) accounted for 13%

(9/46) of the envenomations, tiger snakes for 4% and whip snakes for 4%.

The CSL snake venom detection kit successfully identified the snake responsible in only 42% of envenomated patients on whom the test was run.

5) Seasonality of snake envenomation of domestic animals

Lewis (1978) reports a strong seasonal influence on the incidence of snake bite in reviewing cases (total 351) reported to CSL over the 9 year period 1969-1978 with peak incidence in February-March and October-November.¹⁸ Our figures presented below also demonstrate a similar seasonality, with highest incidence of snake envenomation occurring in the months October and February:

YEAR	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL
1983	9	5	1	2	0	0	2	1	4	5	4	3	36
1982													
1981	12	12	5	4	2	0	0	1	1	11	5	9	62
1980													
1979	7	10	10	8	0	0	0	1	6	8	7	10	67
1978													
TOTAL	23	31	20	13	4	0	0	4	8	23	17	23	155
%	15%	17%	11%	7%	2%	0	0	2%	5%	15%	11%	14%	

* = Corrected percentage as the period 16/12/88-2/5/91 over-represents cases from 12th December through to 2nd May

IV. The Incidence of Snake bite in humans

Sutherland and King (1991) estimated there were about 3000 human confirmed or suspected cases of snakebite in Australia each year of which about 300 required antivenom. The number of reported cases fell from 189 in 1979 to 109 in 1983. Between 1981 to 1991 18 people died, 11 due to brown snake envenomation. Between 1992 to 1994 12 people died, 6 as a result of brown snake envenomation⁵. There has been a fall in the number of human envenomations in the last 10 years

V. Venom

1) Yields and Potency

The table presented below, taken from Sutherland 1983¹ and Masci et al 1998², presents the various venom yields of the different Australian dangerous elapid snakes:

SNAKE	LD50 m g/kg (mice)	Av. Venom Yield mg of dry venom	Max. Venom Yield mg of dry venom
Pseudonaja textilis (eastern brown)	0.041	4	67.2
Pseudechis australis (mulga or king brown snake)	1.91	180	600
Pseudechis porphyriacus (red-bellied black snake)	2.52	37	94
Notechis scutatus (mainland tiger snake)	0.118	35	189
Acanthophis antarcticus (death adder)	0.4	84.7	235.6
Oxyuranus scutellatus (taipan)	0.064	120	400
Oxyuranus microlepidotus (small scaled or Fierce snake)	0.01	44	110
Tropidechis carinatus (rough scaled or Clarence River snake)	1.09	5.5	9.8
Austrelaps superbus (copperhead)	0.5	25.9	84.6
Cryptophis nigrescens (the small eyed snake)	2.67	5	30
from Sutherland 1983			
Pseudonaja textilis Eastern brown from S.A.	0.041	4.41	16.88
Pseudonaja textilis Eastern brown from Qld	0.041	8.14	51.82
Pseudonaja nuchalis (western brown or Gwardar)	0.388	15.01	32.92
Pseudonaja inframacula (peninsula brown snake)	0.25	24.41	76.21
Pseudonaja affinis (dugities W.A.)	0.56	18.12	52.58
from Masci et al 1998			

Note: The LD50 figures presented from Sutherland 1983 are for venom diluted in 0.1% bovine serum albumin in saline as the lethality of some venoms increases when 0.1% bovine serum albumin in saline is used instead of saline alone.¹

The amount of venom injected by a snake into victim may vary widely from the average yield obtained at “milking” a captive snake for a variety of reasons including:

- 1) Domestic animal and human victims are often bitten multiple times
- 2) The amount of venom produced by a snake during a defensive bite (aggravated by a dog or cat or inadvertently stood upon) is far greater than that produced by milking.² The converse was held to be true until quite recently.¹
- 3) Geographical variation may produce considerable variation in venom yield within the same species²
- 4) The hunting experience and athletic agility of the domestic animal “victim”
- 5) The size of the snake. For instance, although baby brown snakes contain enough venom to kill 2 adult humans their small fang size makes it unlikely they can administer an effective strike.

2) Susceptibility to Venom

Kelloaway 1931⁶ described the certainly lethal subcutaneous dose of *Pseudonaja textilis* (common brown snake) venom in the various animals:

Species	Lethal dose Black snake venom mg/kg	Lethal Dose Brown snake venom mg/kg
horse		0.02
sheep		0.02
guinea pig		0.25
cat	7.00	0.1
wild rabbit		0.2
monkey		0.2
rat		0.6
mouse	252	1.2

3) Composition of Venoms

Snake venom is composed of an array of toxic and other non-toxic substances that are mainly proteinaceous. There is considerable variation between species in the volume, composition and toxicity of venom. The prime aim of the snake is to immobilise prey rapidly, and the elapid snake venoms in particular contain a species-specific array of potent neurotoxins, myotoxins, procoagulants, haemolysins, cytotoxins as well as other substances to achieve this end.

Venom components include:

1) Low molecular weight substances including the purines adenosine, adenosine 3 phosphate, guanosine, lymphotoxic factor, smooth muscle stimulant, sensory nerve ending toxin, capillary permeability factor, heat stable anticoagulant. It is thought that these substances diffuse from the bite site quickly and are responsible for the pre-paralytic signs of envenomation such as vomiting, salivation, hypotension, temporary collapse and mydriasis

2) Various enzymes including hyaluronidase (not *pseudonaja* spp), phospholipase A (enhances lysis by haemolysin), phospholipase B (can indirectly lyse red cells esp Mulga & tiger snakes), cholinesterase, L-amino acid oxidase, phosphodiesterase, caesinytic enzymes.

3) Procoagulants and Coagulants. Many of the Australian snakes venoms have procoagulant and coagulant activity:

- High activity occurs with taipan, brown, tiger and mulga snakes
- Mild coagulopathy occurs with death adder
- Coagulopathy of unlikely clinical significance occurs with fierce snake and sea snake venoms
- Snakes unlikely to induce a coagulopathy unless severe envenomation occurs include black, Clarence River snake, and the small eyed snake

Recent human fatalities after snake bite including deaths due to cerebral haemorrhage has led to renewed interest in the pro-coagulant activity present in snake venoms especially brown and also taipan and tiger snakes venom.^{2,7,8} These toxins are prothrombin activators which convert prothrombin into

thrombin, a consumptive coagulopathy rapidly ensues and the blood is unable to clot due to afibrinogenaemia and thrombocytopenia. Bleeding may ensue (at the bite site, into the aqueous humor of the eye, tracheobronchial tree) although it is unusual for victims to bleed severely. CSL antivenom does not easily reverse the coagulopathy that occurs in brown snake envenomated dogs and humans. The doses required are much higher than that required to neutralise the neurotoxins.⁷

P. textilis has 2 prothrombin activators which differ in their requirement for phospholipid both with a molecular weight of around 190kD. Electrophoretic and Western blotting analysis of *Pseudonaja* species venoms show low avidity of CSL brown snake antivenom for the prothrombin activator component (190kD) than compared with other venom components for which it has high avidity, including the pre-synaptic neurotoxin textilotoxin (88kD) and the smaller post-synaptic toxins.²

Maschi et al 1988 have shown that prothrombin activator constitutes 30% of *P. textilis* venom and a concentration of 2ug/ml of *P. textilis* whole venom will clot citrated plasma in 10 seconds. Importantly Maschi et al 1998 performed an in vivo study in rats that clearly demonstrates 8ug of purified *P. textilis* prothrombin activator given IV uniformly killed rats in less than a minute. Interestingly the prior anticoagulation of rats with 100units of sodium heparin before administration of 64ug IV dose of *P. textilis* prothrombin activator resulted in no deaths. They also demonstrated that by administering *P. textilis* prothrombin activator slowly, a tolerance was induced and up to 16x the lethal dose (128ug/rat) cause only 1 in 5 rats to die.

The rapid intravenous injection of any procoagulant can cause a quick death from intravascular coagulation and respiratory failure.⁹ Slow release from a depot into the blood stream results in a coagulopathy and intense secondary fibrinolysis in the case of *P. textilis* venom.²

Of clinical importance is the observations by Maschi et al 1998 that CSL Brown Snake antivenom incubated with purified *P. textilis* prothrombin activator takes at least 15 minutes to start to neutralise the prothrombin activity. Furthermore with no incubation even when mixed in a ratio of 20:1 there is still a residual procoagulant activity of 40% the initial level which remained even after 30 minutes incubation. Not only does CSL brown antivenom have poor affinity for prothrombin activator but the neutralisation interaction is time dependant and occurs slowly. Thus delays in administration of antivenom to patients showing signs of envenomation can be clearly deleterious.

Although a severe coagulopathy (prolonged APPT, PT, low fibrinogen) following tiger snake envenomation is common in dogs, cats do not develop a coagulopathy other than a possibly slightly prolonged APTT. Compared to dogs though, cats have much higher post-envenomation CPK rises.¹⁹

4) Neurotoxins.

Neurotoxins are the most important component in all the Australian elapid snake venoms (except the Mulga snake). Envenomated prey become paralysed and ultimately death usually ensues because of ventilatory failure due to the action of neurotoxins, although myotoxins ultimately achieve the same effect. Both presynaptic and post synaptic neurotoxins are present in venoms.¹

Pre-synaptic neurotoxins

These are relatively large toxins that interact with the cytoplasmic membrane of the terminal boutons especially of the motor nerves of the somatic nervous system and interfere with the cycling of synaptic vesicles. Small microstructural alterations in the presynaptic membrane occur, so called omega shapes or "frustration vesicles" which can be demonstrated clearly with electromicroscopy. Examples include: - textilotoxin MW 88,000 in *Pseudonaja textilis* (common brown snake) venom accounts for 3% of the dry weight of the venom yet 70% of its lethality. It has an IV LD50 in mice of 1ug/kg. It is composed of 4 subunits. It has no appreciable effect on muscle or acetylcholine receptors, resting membrane potentials or nerve conduction, rather, it blocks the release of acetylcholine, and this is largely due to the

phospholipase activity of textilotoxin

- **taipoxin** MW 45,600 (a sialoglycoprotein which is composed of 3 subunits consisting of 120, 120 and 135 amino acid residues) found in *Oxyuranus scutellatus* (taipan) venom. It constitutes 17% of the venom by weight. It has an LD50 in mice 2ug/kg

- **notexin** MW 13,574 (119 amino acid residues in a single chain cross linked with 7 disulphide bonds) in *Notechis scutatus* (tiger snake) venom. This toxin is also a strong Ca^{2+} dependant myotoxin and is a potent phospholipase A_2 . It has an LD50 in mice of approx 6ug/kg

- **notexin 11-5** in *Notechis scutatus* (tiger snake) venom.¹

- **pseudexin** MW 16,500 (a single polypeptide chain) found in *P porphyriacus* venom (red bellied black snake). This toxin accounts for 25% weight of the whole venom. It has phospholipase A activity. Its LD50 in mice by intraperitoneal routes 0.48mg/kg.

Post-synaptic neurotoxin

The post-synaptic neurotoxins found in elapid venoms tend to be polypeptide toxins of low molecular weight that can quickly associate with target receptor sites and as a rule are quickly reversed with the administration of appropriate antivenom. For instance:

In tiger snake venom, two post synaptic neurotoxins are found: toxin 1 (60 aa residues MW 6,000) and toxin 2 (70aa residues MW 7,000) with LD50 in mice of 100ug/kg and 150ug/kg respectively. These toxins are fast acting, all animals died within 2 hours of injection.

In brown snake venom the postsynaptic neurotoxin, pseudonejatoxin, occurs. It is unusual as it is larger than most (117aa residues MW 12280) and causes irreversible blockade by firm binding to acetylcholine receptors. The IP LD50 in mice is 300ug/kg.

Electrophysiological studies^{15,16} in humans envenomated by the New Guinea taipan closely correlate with the clinical condition and may have a role in assessment of interventions in the management of snake bite victims. Nerve conduction velocities do not alter in envenomated patients. Repetitive nerve stimulation studies reveal decremental responses with post-tetanic potentiation followed by post-tetanic exhaustion. These findings are consistent with the neuromuscular synapse as the major action of the taipan neurotoxins. The compound muscle action potential (CMAP) amplitudes declined over the first 2-4 days subsequent to envenomation and gradually increased in parallel with clinical recovery. Repetitive stimulation studies revealed a consistent brief potentiation of the CMAP followed by a significantly greater decrement than observed at rest. This effect lasted up to 30 minutes and is not altered by IV edrophonium. Single muscle fibre EMG recordings during the recovery phase of envenomation were abnormal with marked blocking and increase jitter.^{15,16}

5) Haemolysins

The haemolytic activity of the dangerous Australian elapid snakes is less important than the effect of the other venom components. If haemolysis does occur it is unlikely to cause a significant anaemia, and a haemoglobinuria may follow but this is often overshadowed by concurrent myotoxic action of venoms and resultant myoglobinuria and dark urine.

The strongly haemolytic venoms include the genus *Pseudechis* (black snakes) especially the red bellied black snake (*P porphyriacus*) and copperhead (*A superbus*). *P nuchalis* can cause clinical haemolysis.

Only weak haemolysins are in Taipan, fierce, death adder and common brown snakes.¹

6) Myolysins and Cytotoxins

Many of the dangerous Australian elapid snake venoms have a significant myolysins in their venoms. Rhabdomyolysis, myoglobinuria and resultant acute tubular necrosis and renal failure are a well recognised occurrence in snake envenomated patients especially cause by the sea snake *Enhydrina schistosa*, mulga snake *Pseudechis australis*, tiger snake and taipan. In the case of the latter 2 it is their main neurotoxin that is responsible of their venoms myotoxin action ie both notexin and taipoxin are potent myotoxins.

Several people have survived a number of days following snake envenomation only to die from renal

failure days after the bite.

The mulga snake (king brown) *Pseudechis australis* is the most prolific venom producer of all the Australian snakes. The venom contains mulgotoxin (MW 13,484 consisting of a single polypeptide chain of 122 amino acid residues and cross linked by 7 disulphide bonds). This toxin has an LD50 in mice of 0.2mg/kg. As opposed to all the other Australian elapid snakes this Mulga snake venom has no neurotoxic activity, rather mulgotoxin is a potent myotoxin.¹

Cardiac muscle toxins are present in many New Guinea and Australian snakes including papuan black snake, taipan, death adder and brown snake. The action of these toxins is thought to be a direct toxic effect of a venom component upon cardiac myocyte function. ECG reveals bradycardias including atrioventricular block and septal T wave inversion. Taipan venom contains a Ca channel blocker, taicatoxin. Only a few patients (8.3%) actually had evidence of myocardial damage (elevated plasma troponin T).¹⁰

In dogs, tiger snake venom does not significantly affect cardiac or smooth muscle histologically whereas skeletal muscle damage is patchy but serious. The severity is influenced by dose, and interestingly, immobilisation under general anaesthesia resulted in significant protection against the myolytic action of high doses of venom.¹⁷

Lewis (1994)¹⁷ reports acute tubular necrosis and deposition of a proteinaceous material in renal tubules on studies of the effects of tiger snake venom in dogs, indicating a direct nephrotoxic effect which would be complicated by the myotoxin damage of skeletal muscle and myoglobinuria. These findings emphasise the need for supportive treatment (IV fluids) aimed at maintaining renal function in envenomated dogs.

VI. Antivenom

1) Potency of Antivenom

CSL base their dosage recommendations on a bioassay performed in guinea pigs. 1 unit of antivenom should neutralise 0.01mg of venom. The potency of the antivenom is determined by the measuring the amount of antivenom needed to prevent death when known quantities of venom are administered to guinea pigs. As mentioned before, species vary in their susceptibility to venoms and it maybe that guinea pigs are particularly susceptible to components of the antivenom other than the procoagulant, thus making this an inadequate assay for the determining the dose of antivenom required to neutralise the procoagulant effects of venoms in dogs, cats and man.

2) Source of Antivenom

Commonwealth Serum Laboratories (CSL) antivenoms contain a highly purified light chain portion (Fab') of IgG prepared from plasma harvested from hyperimmunised horses (percherons). The antibody fraction is separated by migration in a cephodex column, then the immunoglobulin is enzymatically cleaved using papain and the antigen specific light chain fraction retained.

The Australian Veterinary Serum Laboratory at Lismore produce a brown, tiger and combination brown tiger antivenom prepared from hyperimmunised blood hounds.

There are several references in contemporary literature dealing with viper bites of humans in Africa demonstrating that Fab antivenom prepared from hyperimmunised sheep has the advantages of a more rapid tissue penetration and larger apparent volume of distribution (i.e. the volume of (tissue) fluid in which the antivenom would be uniformly distributed to achieve the observed plasma concentration)^{3,11}.

3) Recommended Dose

One vial of CSL antivenom will neutralise in vitro the average venom yield. However as shown

above an envenomated animals may receive a dose that may vary considerable from average. Some animals are often sublethally envenomated due to agility e.g. cats. Sometimes snakes may deliver many times the “average” dose, especially if they are delivering a defensive bite rather than that produced by “milking”. Snakes may also inflict multiple bites on an animal. There are within species and seasonal differences in venom potency and volume, and possibly brown snakes, like sea snakes¹, may regulate the amount of venom they inject.²

Animal patients may develop coagulopathies, especially those envenomated by brown snakes, and may require multiple vials of antivenom well in excess of that required to reverse the neurotoxin components of the venom.^{2,7} Patients for whom treatment has been delayed may also require more than the initial recommended dose of antivenom. CSL also states that if symptoms and signs of envenomation are already present, at least twice the recommended dose of antivenom should be infused.

For severely envenomated patients, especially brown snake but also Mulga snake envenomations we have had to administer multiple vials of antivenom, 5,500units of brown antivenom was required to bring about a successful outcome in one of the patients presented in this review period.

Recommended initial dose of antivenom when a snake has been identified²³:

SNAKE	ANTIVENOM
Tiger snake	Tiger snake antivenom 3000units
Tasmanian Tiger Snake	Tiger snake antivenom 6000units
Chappell Island Black Tiger Snake	Tiger snake antivenom 12000units
Death Adder	Death Adder Antivenom 6000units
Taipan	Taipan antivenom 12000units
Small-scaled or Fierce snake	Taipan antivenom 12000units
Copperhead	Tiger snake antivenom 3000-6000units
Brown snake	Brown snake antivenom 1000units
Dugite	“ “
Gwardar	“ “
	Mildly envenomated cats may initially require only 500units
Red bellied black snake	Tiger snake antivenom 3000units or Black snake antivenom 6000units
King brown or Mulga snake	Black snake antivenom 18000units
Rough scaled or Clarence River Snake	Tiger snake antivenom 3000units
Papuan Black Snake	Black snake antivenom 18000units
Sea Snakes	Sea snake antivenom 1000units Tiger snake antivenom 3000units

Recommended initial dosage of antivenom when identity of the snake is uncertain²³:

STATE	ANTIVENOM
Tasmania	Tiger snake 6000units
Victoria	Tiger 3000unit & Brown 500unit combined antivenom
NSW, Queensland, SA, WA, NT, Papua NG	Polyvalent snake antivenom

VII Clinical Signs of Snake Envenomation

Variability

All lethal envenomations by the dangerous Australian snakes will usually ultimately end in the flaccid paralysis of the victim, but there are considerable variations in the clinical course of signs of

envenomation depending on species of snake, species of victim, the envenomating dose and where it was delivered.

Pre-paralytic signs

The rapidity of onset of the signs of snake envenomation is related to the dose of venom received.

Onset of symptoms of evenomation in dogs (1-2 hours¹², 6.5 hours²¹) is faster than the onset for cats (15 hrs²¹). Dogs often show preparalytic signs such as transient collapse, vomiting, salivation and lethargy, whereas cats infrequently display such premonitory signs, rather the earliest signs usually seen are weakness and ataxia. The occurrence of preparalytic signs almost invariably indicates the patient has received a lethal dose of venom.

Time for onset of signs of envenomation and death

Death following a multilethal dose of venom can ensue rapidly especially if the venom is injected in an area of the body with a rich blood supply and lymphatic drainage such as the face. Lewis 1994 has shown that in dogs given a multilethal dose of tiger venom, preparalytic signs developed within 5-30 minutes, mydriasis in 2-4 hours and severe paralysis and death within 2.5 to 5 hours. In our case series several brown snake envenomated dogs have required ventilation within 1 hour of receiving a snake bite. Again, envenomated cats have a longer period between snakebite and death^{21,18}, up to 43 hours¹². One brown snake envenomated cat in our case series took at least 24.5 hours between time of presentation and onset of a serious envenomation, which required multiple doses of antivenom and mechanical ventilation for 8 hours to save its life.

Cats

Clinical signs of envenomation are varied and inconsistent. Weakness and ataxia are often the earliest signs of envenomation. Moisisidis et al (1995) examining brown and tiger snake envenomation in cats state that "Other signs such as mydriasis, vomiting and the absence of pupillary reflex were inconsistent, transient, not species specific and could easily be overlooked by most owners."¹²

Signs of envenomation include generalised weakness, hindlimb paresis, depression, ataxia, vomiting, absent pupillary light reflex, mydriasis, tachypnoea, dyspnoea, intermittent weak struggling, depression and disorientation, pharyngeal paralysis, haematuria, coma, and bleeding from the bite wound. Often cats are presented with a generalised flaccid paralysis except for the ability to still move their tail and a plaintive vocalisation.

Dogs

Envenomated dogs can show even more diverse signs than cats. Pre-paralytic signs are common. Owner histories often relate that although the dog collapsed soon after he was bitten, he/she has recovered and now is able to walk, run (even eat and drink), must be regarded as portentous of an impending severe envenomation.

Signs of envenomation include vomiting, occasionally haematemesis, haematoptysis, severe trembling, salivation, excitement, weakness, mydriasis, defecation, posterior paresis progressing to a generalised flaccid paralysis, cyanosis and death.

Horses

Similar to dogs and cats, signs of envenomation are diverse and vary depending on species of snake involved. Signs of envenomation include muscle tremor, fidgety, sweating, attempting to lay down, but standing again and wandering around in a compulsive manner, trying to walk to dams, head pressing, salivation, tongue and pharyngeal paralysis, mydriasis, absence of pupillary light reflex, yet menace reflex may still be present. Ultimately hindquarter paralysis occurs progressing to generalised flaccid paralysis. Haematuria may occur and dyspnoea progressing to respiratory paralysis

Predicting clinical events



Apart from the importance of the occurrence of pre-paralytic signs and the rapidity of onset of clinical signs if the snakebite was witnessed, the severity of an envenomation is difficult to predict. All suspected snakebite patients must be observed closely for a minimum of 24 hours.

Do circulating levels of venom and antivenom reflect clinical events? For envenomated patients that have a long time lag between snakebite and treatment, the irreversible binding of presynaptic neurotoxin means there is unlikely to be a good correlation. However a more rapid bedside test for detection of venom levels would be a welcome addition to assessing the progression of envenomated patients and the requirement for additional antivenom.

VIII. Treatment

In implementing treatment it is of vital importance to recognise the diverse range of clinical envenomation scenarios as well as the fluidity of any envenomated patient's status. Envenomated animals may present without any clinical signs of envenomation, then be on the brink of death 30 minutes later. Clinical scenarios may range from a mildly quadriparetic cat that may well require only intravenous fluids and supportive care for a few days, to a cat or dog that is collapsed presenting with cyanosis, respiratory arrest, bradycardia, generalised neuromuscular flaccidity and a life threatening coagulopathy that requires a prompt integrated response for successful resuscitation.

The mainstay of therapy for the treatment of snake envenomation in domestic animals is the same as that for human patients ie the prompt provision of adequate amounts of the appropriate antivenom.

- IV fluids

All cases which were to receive antivenom, and nearly all envenomated cases which were hospitalised yet not given antivenom, had an intravenous catheter placed and secured and were administered IV fluids, usually Hartmann's solution, given at a maintenance rate.

Fluids are indicated to correct any existing dehydration, maintain normovolaemia and thus blood pressure and cardiac output, maintain glomerular filtration and assist in offsetting possible renal toxicity due to myoglobinaemia.

- Pretreatment

Antihistamine. Prior to administration of antivenom all cases were pretreated with the antihistamine chlorpheniramine maleate 1mg/kg intravenously (the use of phenergan was associated with the death of a cat in this case review) and

Adrenalin 10ug/kg (Dilute 1:1000 1ml ampoule in 10ml sterile saline and dose 0.1ml/kg) subcutaneously. Do not give the adrenalin intravenously. 8 human patients have died in the last 12 years as a result of cerebral haemorrhage partly because of the coagulopathy and concomitant hypertension (due to a sympathetic response). Interestingly hypertension is part of the clinical syndrome in humans of all funnelweb spiderbite and most red-back spiderbite victims.

- Antivenom

The indications for the need of antivenom include:

- a) Occurrence of pre-paralytic signs (vomiting, initial collapse, salivation, mydriasis, trembling) as this indicates an almost invariable potentially lethal envenomation has been delivered
- b) Progressive flaccid paralysis, weakness or muscle tremors
- c) Dogs unable to stand with flaccid quadraparesis on presentation
- d) Hypoventilation
- e) Serious coagulopathy. Bleeding from the bite site and venipuncture sites, gingival petechiae, hyphaema, extended clotting times, low fibrinogen and platelet numbers (ie consumptive coagulopathy)

Following the above recommendations for the selection of antivenom, the appropriate antivenom is diluted in 4-10x its volume with sterile saline or Hartmann's solution and administered slowly over 20 minutes. It is only given more rapidly if the animal is in extremis.



Antivenoms can bind complement and produce an anaphalactoid reaction in patients with no prior exposure to equine globulins, hence the recommendation for pre-treatments, dilution and slow administration

- Supplementary Oxygen

Many envenomated animals are hypoxic and require supplementary oxygen e.g. nasal oxygen catheter flows 200-500ml/min of humidified oxygen will create an inspired oxygen concentration of 50-60%

- Ventilation

In this case series 24/104 (23%) patients that were treated developed respiratory failure and required intubation and ventilation in addition to the provision of adequate amounts of appropriate antivenom. Not infrequently both envenomated cats and dogs in respiratory failure make weak struggling efforts which may become stronger after they have been intubated and are being ventilated. On extubation (despite nasal oxygen administration) they may rapidly go into respiratory failure again. To control any struggling whilst being ventilated several methods can be employed:

- background (low) dosage of methadone (0.1-0.2mg/kg) and or diazepam (0.1-0.2mg/kg),
- connect your ventilator by way of a long piece (2-3 meters) of 22mm corrugated gas tube to the connection for the rebreathing bag on your anaesthetic machine and provide 0.25 to 0.5% isoflurane

and normal fresh gas flows.

If using isoflurane it will be necessary to turn the vaporiser off every hour or so and evaluate the animals efforts at spontaneous ventilation to determine when to extubate. In animals that have not been sedated, when struggling efforts resume, if sufficiently strong, and if accompanied by strong spontaneous respiratory efforts, they may be extubated.

The use of humidified inspired gas for ventilation is important, especially for animals ventilated for more than 1hour. Also animals that require ventilation for longer periods should be given a blended gas mixture of maximum oxygen concentration 40%.

Cats should be ventilated at a rate of 15-25 breaths/min with a peak inspiratory pressure of 10-15 cm water and if capnography is available an end-tidal CO₂ of 20-30mm Hg. dogs should be ventilated at a rate of 10-20 breaths/min with a peak inspiratory pressure of 15-20cm water and end-tidal CO₂ of 30-40mm Hg

- Hospitalisation

Immobilisation is an important part of first aid for both the human & domestic pet snakebite victim. Keeping an envenomated animal quite delays the systemic absorption of venom and may help minimise myotoxic effects of tiger snake venom¹⁷ and the effects of procoagulant in brown and taipan venom²

Even animals only suspected of being bitten by a snake should be hospitalised and kept under observation for at least 24 hours. For cats, the period between the snakebite and onset of envenomation may at least 24 hours.

- Additional Drugs

Atropine is not infrequently required in some of our cases of snake envenomation to treat for bradycardia, AV blocks and excessive bronchial secretions.

Furosemide is also occasionally required to assist with the treatment of pulmonary oedema.

Antibiotics are routinely administered to envenomated patients. We have seen several cases of pyothorax in cats approximately 1-2 weeks following recovery from envenomation.

IX. Clinical Pathology Evaluations

1) The CSL Snake Venom Detection Kit

The Commonwealth Serum Laboratories Snake Venom Detection Test Kit (SVDK) is an ELIZA test that can be used on swabs taken from the patient's bite site, blood or urine. CSL states the test has a sensitivity down to 10ng venom/ml of sample tested.



Conflicting reports exist in the medical literature on false negative test results with the use of the CSL SVDK in envenomated patients. Mead (1996) report negative result in 4 out of 14 definitely envenomated children ie 28%.¹³ Trevett (1995) in New Guinea report that SVDKs detected venom from bite sites in 39/46 envenomated patients, giving a false negative result in 15% of patients.¹⁴ Sutherland (1992) reports that over a one year period in Australia (1989-1990) SVDKs were used in 181 cases of snake bite and reported as being useful in selecting appropriate snake antivenom in 31% of cases of antivenom use.

In our own practice in the 24 month period 1/10/80-1/10/82 the CSL snake venom detection kit identified the responsible snake in 2 out of 5 definitely envenomated patients. In the 28 month period 1989-1991 10 cases out of 17 definitely envenomated patients on whom CSL SVDK tests were performed gave false negatives (59%). Similarly, in the 36 month period 5/9/96-5/9/98 at South Tamworth Animal Hospital, 11 CSL SVDK tests were performed in envenomated animals, 6 gave negative tests (55%). And in 2 of these occasions, the identity of the offending snake was confirmed by morphological examination. Summing these 3 periods, the CSL SVDK was used 33 times and gave a positive result in 14 of these (42%).

Some false negative CSL SVDK can be explained by the variation of venom levels found in blood and urine. 8 hrs after a snake bite blood levels of venom are likely to be below the detectable level of the SVDK and testing of urine is recommended. There are differences in detection depending on the snake species involved:

A lethal dose of Tiger snake venom (0.1mg/kg) administered subcutaneously to cats achieved peak blood levels at 2 hrs, fell quickly by 6 hrs and was undetectable by 10-12hrs. Whereas venom was undetectable in urine until detectable urine levels appeared at 6-8 hrs, peaked at 16 hrs and then gradually declined to low levels by 24 hrs.

A lethal dose of brown snake venom (0.4mg/kg) administered subcutaneously to cats achieved similar peak blood levels by 2 hrs and gradually declined to an undetectable level over 24 hrs. Venom levels in urine followed that of blood with an almost immediate progressive rise to peak at 8 hrs and gradually fall to undetectable levels by 28-40 hrs.¹²

Because of the large percentage of false negative results with the CSL SVDK, it is important that a negative test result in an as yet symptomless patient is not regarded as proof of the absence of a potentially lethal envenomation ie the "more fright than bite" interpretation. A negative test maybe meaningless.

2) Other Laboratory Evaluations

1) Clotting times, fibrinogen levels & platelet counts

For the snake venoms with strong procoagulant activity, the coagulaopathy they create precedes the action of the neurotoxins (e.g. brown and taipan venoms). The procoagulants can kill in their own right.²

In the treatment of severely envenomated people, the 4 hourly measurement of fibrinogen is recommended as a guide to adequacy of the amount of antivenom administered, although there is a lag phase until the liver starts to reconstitute fibrinogen.

In the case of uncertain diagnosis and in severe envenomations, tests of coagulation may be very helpful. Such tests include whole blood activated clotting time, prothrombin time, activated partial thromboplastin time, fibrinogen and platelet count (the later 2 fall with the intravascular activation of thrombin and the resultant consumption of fibrinogen and platelets). Several of the cases reported in this series had PT and APTTs > 180 seconds. About half of dogs envenomated by a tiger snake will have elevated circulating fibrin degradation products. In the case of cats with tiger snake envenomation, they are unlikely to show abnormal clotting times¹⁹

2) Haematocrit and Total Plasma Proteins

Measurement of PCV and TPP is quite helpful not only in the assessment of the state of haemoconcentration but also in evaluating the presence or absence of haemolysis

3) Urinalysis

In the case of envenomation by any of the black genus, tiger snake and also any serious envenomation by any species of snake, urinalysis is helpful in assessing renal function and the degree of myotoxic damage by way of the presence or absence of haemoglobin & myoglobin, proteinuria, casts and specific gravity. Stress glycosuria can be observed in some envenomated cats

4) Urea, creatinine and electrolytes

In the case of envenomation by any of the black genus, tiger snake and also any serious envenomation by any species of snake particularly if there is a protracted clinical course, testing renal function may be important as renal failure can occur as a result of snake envenomation

5) Serum enzymology

Myotoxic and cytotoxic activity of many venoms will often elevate serum levels of CPK, AST (SGOT), LHD and myoglobin.

X. Treatment Outcomes

1) Survival of snake envenomation patients with and without treatment:

Referral	Species				Snake NTK				Snake TK			
	cat	dog	horse	Tot	cat	dog	Tot	cat	dog	horse	Tot	
1089	24	12	0	36	13*	24	37*	181	78	-	259	
1082												
1628	39	22	1	62	610*	36*	916*	249	156	11	416	
2591												
5995	45	22	0	67	2831*	47*	3038*	1314*	145*	-	2129*	
5993												
TOTAL	108	56	1	165	344	917	4261	564	369	11	9204	
%	65%	34%	1%	10%	75%	53%	69%	88%	92%	10%	88%	

* = 1 patient euthanased.

The chance of both dogs and cats surviving a snake envenomation is significantly greater if treated with antivenom. In the case of cats the chance of survival if not treated is 75% vs 86% if treated, and for dogs, if not treated the chance of survival is 53% vs 92% if treated.

In interpreting the above results several strong biases must be recognised. There are many factors that influence veterinarians on whether to treat with antivenom or not⁴. Case selection by the Veterinarian based on severity of symptoms will strongly bias survival results for both treated and untreated groups:

a) Many envenomated animals, in particular cats, do not receive a lethal envenomation. Several reasons have been presented to account for this including agility^{18,21}, experience and the fact that cats have a higher per unit body weight tolerance to snake venoms^{6,21}. From the above figures it seems we have

developed a bias in the last 3 years not to treat (and perhaps delay antivenom treatment of) cats, possibly based on our experience of their higher likelihood of survival, although this obviously for some patients this may result in a fatal outcome.

b) For patients where owner consent to treat was obtained, those with more severe symptoms are more likely to receive antivenom

c) Owner financial and emotional considerations confound the results:

- Not all owners gave permission to administer antivenom, thus some untreated individuals that have received a lethal envenomation will die.

- Several animals were euthanased at the owners request in both treated and nontreated groups

d) Many envenomated animals may die without every reaching a Veterinary practice

e) Despite the knowledge that approximately 70% of envenomated animals have been bitten by a brown snake in our practice, there is no doubt that some animals, because they were given the wrong antivenom.

2) Survival of patients treated with antivenom when identity of snake was known vs unknown

For those patients that received antivenom, the table below compare survival outcomes of two patient groups, those in which the identity of the snake is known vs those in which the identity of the snake is unknown

PERIOD		TREATED PATIENT'S SURVIVING/TOTAL TREATED PATIENT'S					
		SNAKE SPECIES					SNAKE SPP UNKNOWN
		BROWN	BLACK SPP	MULGA	REDBELLD BLUEBELL	SVDK+ive	TIGER TOTAL
1/10/80-	DOG	2/2					2/2 5/6
1/10/82	CAT	3/4					1/1 4/5 14/16
16/12/88-	DOG	7/8				1/1	1/1 9/10 6/6
2/5/91	CAT	2/2	1/1			1/1	4/4 19/25
	HORSE		1/1				1/1
5/9/95-	DOG	9/10*	1/1	1/1			11/12 3/3
5/9/98	CAT	4/4					4/4 9/10*
TOTAL	DOG	18/20	1/1	1/1		1/1	22/24 (92%) 14/15 (93%)
	CAT	9/10	1/1			1/1	12/13 (92%) 42/51 (82%)
	HORSE	9/10	1/1				

* = 1 patient euthanased at owners request

Across all snake envenomation cases of all severities there is no statistical difference in patient survival with knowing the identity of the offending snake in the case of envenomated dogs, whereas there is for cats ($P > 0.5$). As 72% of the identified cases of snakebites in our district are due to brown snakes, we have a good chance of survival by treating with the monovalent antivenom for brown snake envenomation. With severely envenomated patients, positive knowledge of the offending snake is crucial to survival as often multiple vials of antivenom are required to treat such patients. Simply in light of costs, neither owner nor veterinarian is going to feel comfortable putting multiple hundreds of dollars worth of

antivenom into a patient when the identity of the offending snake is uncertain.

3) Outcome of severely envenomated patients that required mechanical ventilation

Over the 3 review periods a total of 24/104 envenomated patients required mechanical ventilation. Respiratory failure that required mechanical ventilation was recognised clinically by several methods:

- A cyanosed patient not responding to supplementary oxygen administration
- Clinical assessment of serious hypoventilation. This includes cases that are severely paralysed and cannot perform an adequate inspiration and also patients that may be making respiratory efforts but the presence of bronchial or pulmonary oedema hampers gas movement and or exchange, or various combinations thereof.
- Hypoventilation & cardiac rhythm disturbances (bradycardia is common).

Ventilators used in our practice over the years of the review periods for providing mechanical ventilation for severely envenomated patients include Bennet Model PR2, Bird Mk14, Bird IMV with CPAP.

DATE	CASE	SPECIES	BREED	AGE	IPPV	SNAKE	ANTI-VENOM	COMMENT	LIVE/DEAD
				yrs	hrs				
5/12/81	Sam	C	Bull terrier	6.5	0.1	Brown	1000Br	Apnoea on arrival 3m ins after antivenom started spont ventilation	L
23/1/82	Beaven	F	Dom sh	1.5	.5	-	1000Br	Nasal O2, 6hr after Tx cyanosed. Died after 30m in IPPV	D
11/10/80	Candy	C	Dachshund	11	1	-	1000Br		D
4/3/81	Whisks	F	Dom sh	-	.3	Brown	500Br	Flaccidparalysis.PreTx phenegan excitement + arrest. Antivenom + CPR. Euthanasia after 20 mins	D
22/10/89	Bounce	C	Fox Terrier	6	1	Brown	2500Br		L
28/12/90	Muffy	F	Dom sh	3	8.5	-	1000Br +3000Tig	SVDK -	D
19/2/91	Pete	C	Kelpie	8	1.5	-	3000Poly		L
1/12/90	Marco	C	Dalmatian	7	4	Brown	2000Br+3000Tig	SVDK +.W alking.Collapse in 5m in	L
15/10/90	Tippy	C	Kelpie	8	10	Brown	2500Br		D
12/2/90	Buffy	F	Dom sh	2	40	-	3000Br+3000Tig	SVDK -. Dry inspired gas. Bronchopneumonia	D
28/11/89	Moggy	F	Dom sh	6	2.5	-	1000Br	SVDK -. Arrested CPR+Adrenalin+AntiVenom antihis+bicarb+Dex+CaCl	L
22/1/90	Piddles	F	Dom sh	2	0.3	-	1000Br		D
30/10/90	Co-op	F	Dom sh	6	25	-	1000Br + 3000Tig+ 3000Poly	SVDK -	L
29/10/90	Gorbechov	F	Dom sh	0.5	3	-	1500Br + 3000Tig		L
20/10/96	Midge	C	Fox terrier	4	4.5	Brown	3500Brown	SVDK +. Bradycardia HR 20 Tx Atropine. Pulm +Bronchial oedema Tx Lasix + 5cm PEEP	L
24/2/98	Thomas	F	Dom sh	-	0.25	-	1000Br	Euthanasia at owners request	D
26/2/98	Tinker	F	Dom sh	2	39	Brown	2000Br	SVDK +. CPR 13hrs of IPPV Due to ventilator malfunction	L
4/8/98	Amy	C	Jack Russell	6	2.5	Brown	2000Br AVSL	Marked bronchial oedema & Struggling despite resp paralysis IPPV with 0.25-0.5% Isoflurane	L
23/10/97	Zoe	C	Lab	4.5	7	Brown	5500Br	Initial collapse.W alking on presentat -ion.W aited to dog dropped ,then Tx	L
10/3/98	Crunchie	F	Burmese	4	8	Brown	2000Br	SVDK +.Presented trembling,weak hindlim bs.Im proved.24.5hrs later Struggling & resp failure. Tx given	L
26/10/96	Billy	C	Scotty	7.5	8	Mulga	6000Tig+ 36000Black	15m in after bite, presented standing 15m in later Comatose&resp failure	L
29/3/96	Molly	C	Jack Russell	2	.5	Brown	500Br	Euthanasia at owners request	D
13/12/97	Ginger	F	Dom sh	2.5	19	-	500Br	Tachypnoea,recumbant,depressed, myotactic reflexes depressed	L
23/9/97	Missy	C	Kelp	7	2	Brown	2000Br	Rapid deterioration, then after Tx rapid improvement	L
TOTAL & RANGES		12 dogs 12 cats			6m in to 40hr	12brown 1Mulga	If single vial Tx 4/9 lived If multiple vial Tx 12/15 lived	Excluding euthanasia at owners request, If snake i/d known 10/12 lived, if unknown 5/10 lived	9 died, 2 euthanasia 15 lived

Our early experience with ventilating severely envenomated patients was little more than a last ditch effort to save a dying animal, and, as such, held little success. Clinical experience and human literature demonstrated the need to provide not only multiple vials of antivenom but short to medium term mechanical ventilatory support for some severely envenomated animals. Despite having received adequate quantities of appropriate antivenom many envenomated patients develop respiratory failure. The cases presented from the second review period likely reflect the practice's inexperience for this therapeutic modality. 2 of 10 ventilated cases were ventilated with dry gas, both cases developed a bronchopneumonia, one of which died. Subsequently all ventilated animals were administered a warmed inspired gas mixture using an inspired oxygen tension of 40-100%, although animals ventilated longer than 8 hours were supplied gas with an oxygen tension of 40-60%. In the third period of the review, 10 patients were also ventilated, and all survived except 2 that were euthanased at their owners request because of financial considerations.

From the above, it can be seen that severely envenomated animals often require multiple vials of the appropriate antivenom to improve their chances of survival and that envenomated patients in which the identity of the offending snake is not established have a higher risk of death. Furthermore providing mechanical ventilation (for periods of up to 40 hours) of severely envenomated patients that have been given adequate amounts of appropriate antivenom may be required to save their lives.

Appendix 1

1) For the 24 month period 1/10/80 to 1/10/82:

Total number envenomated: 36 consisting of 24 cats (67%) and 12 dogs (33%)
 Proportion of practice case load 0.46%
 Total deaths: 8 died (22%).
 Non treated cases 7/36. Of which a total of 50% survived.
 - 4 died: 2 dogs were dead on arrival. 1 cat euthanased, One cat died on 2nd day of hospitalisation having received IV fluids only
 - 3 survived
 Treated (antivenom) cases 29/36. Of which 86% survived.
 - 4 died, 3 cats and 1 dog
 - 25 survived
 Snake identification achieved in 8/36 cases (22%) : 7 brown and 1 tiger
 - Anatomical identification of dead snake 6/36
 - CSL Snake Venom Detection kit 2/36.
 Frequency of Use of CSL SVDK 5/36. False negative 3/5 (60%)

Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
No. of cases	3	9	5	1	2	0	0	2	1	4	5	4
%	8.3	25	13.9	2.8	5.6	0	0	5.6	2.8	11	13.9	

2) For the 28 month period 16/12/88 to 2/5/91

Total number envenomated: 62 consisting of 39 cats, 22 dogs, 1 horse
 Proportion of practice case load 0.52%
 Total deaths: 13 died (21%).
 Non treated cases 16/62 . Of which 56% survived
 - 7 died: 4 cats and 3 dogs (of which 1 cat and 1 dog were euthanased at owners request)
 - 9 survived (6 cats and 3 dogs)
 Treated (antivenom) cases 46/62 (74%) consisting of 29 cats, 16 dogs & 1 horse

- 6 died, 5 cats and 1 dog (13%).
 - 5/6 of these did not have the offending snake identified
 - 40 survived (87%)
 - Multiple vials of antivenom were required in many of the cases. Single vials of antivenom were used in 24/46 cases (53%)
 - 9 patients received 500units of brown antivenom
 - 18 patients received 1000units of brown antivenom (1 died)
 - 1 patient received 3000units tiger antivenom (1 died)
 - 2 patients received 2,500units of brown antivenom (1 died)
 - 2 patients received 3000units tiger and 500units brown antivenom
 - 7 patients received 3000units tiger and 1000units brown antivenom (2 died)
 - 2 patients received 3000units tiger and 2000units brown antivenom (1 died)
 - 2 patients received 6000units tiger and 1000units brown antivenom
 - 1 patient received 3000units tiger, 1000units brown & 1 polyvalent
 - 1 patient received polyvalent antivenom
 - 12/46 (27%) patients developed respiratory failure
 - 2/46 were given oxygen by nasal catheter and died.
 - 10/46 were ventilated (from 20 mins to 40 hrs) of which 4 died,
 - of these 4, snake identification was established only in 1 case
- Snake identification achieved in 14/62 (22%) of the total cases and 14/46 treated patients (31%)
- Anatomical identification of dead snake 7/46 (6 brown, 1 Mulga)
 - CSL Snake Venom Detection kit 7/46. (4 brown, 1 tiger, 1 Pseudechis spp)
- Frequency of Use of CSL SVDK 17/46. False negative 10/17 (58%)

Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
No. of cases	11	8	3	2		0	0	1	0	10	3	5
Corrected %	20.4	14.8	5.6	3.7	5.6	0	0	2.8	0	27.8	8.3	11.1

3) For the 36 month period 5/9/95 to 5/9/98

- Total number envenomated: 67 consisting of 45 cats and 22 dogs .
- Proportion of practice case load 0.35%
- Total deaths: 10 died (15%).
- Non treated cases 38/67 . Of which 79% survived
- 8/38 died : 5 cats and 3 dogs (of which 1 cat & 1 dog were euthanased at owners request)
 - 30/38 survived (26/31 cats and 4/7 dogs)
- Treated (antivenom) cases 29/67 consisting of 14 cats and 15 dogs
- 2 died, 1 cat & 1 dog. Both were euthanased at owners request due to financial constraints
 - 27 survived (93%)
 - Multiple vials of antivenom were required in many of the cases. Single vials of antivenom were used in 13/29 cases (45%)
 - 12 patients received 500units of brown antivenom (1 died -euthanasia)
 - 8 patients received 1000units of brown antivenom (1 died - euthanasia)
 - 3 patients received 2000units of brown antivenom
 - 1 patient received 2,500units of brown antivenom (1 died)
 - 1 patient received 5,500units of brown antivenom
 - 1 patient received 3000units tiger antivenom
 - 1 patients received 3000units tiger and 500units brown antivenom
 - 1 patient received 6000units tiger antivenom and 18,000units of black antivenom
- 10 out of 29 patients (35%) that received antivenom treatment developed respiratory failure
 - 2/10 were ventilated for a short period then euthanased at owners request
 - 8/10 were ventilated from 15 mins to 39 hrs all of which survived
 - of these 8 snake identification was established in 7 cases
- Snake identification achieved in 24/67 (36%) of the total cases and 16/29 treated patients

- Morphological identification of dead snake in 19/67 cases (16 brown, 3 Mulga, 1 red-bellied black, 1 blue bellied black, 2 whip snakes)
 - CSL Snake Venom Detection kit 5/67. (5 brown)
- Frequency of Use of CSL SVDK 11/67. False negative 6/11 (54%)

Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
No. of cases	7	10	10	8	0	0	0	1	6	8	7	10
%	10.4	14.9	14.9	11.9	0	0	0	1.5	9.0	11.9	10.4	14.9

BIBLIOGRAPHY

- 1 Sutherland SK (1993) "Australian Animal Toxins. The creatures, their toxins and care of the poisoned patient" Pub: Oxford University Press. Melbourne
- 2 Masci PP, Mirtschin PJ, Nais TN, Turnbull rk, Kuchel TR, Whitaker AN (1998) "Brown snakes (*Pseudonaja* Genus): Venom Yields, Prothrombin Activator Neutralisation and Implications Affecting Antivenom Usage" *Anaesth Intensive Care* 1998 26:276-281
- 3 Meyer WP, Habib AG, Onyade AA, Yakubu A, Smith DC, Nasidi A, Daudu IJ, Warrel DA, Theakston RD (1997) "First clinical experiences with a new ovine Fab *Echis ocellatus* snake bite antivenom in Nigeria: randomised comparative trial with Institute Pasteur Serum (Ipser) Africa antivenom. *American Journal of Tropical Medicine and Hygiene.* 56(3) 291-300. 1997 Mar.
- 4 Mirtschin PJ, Masci P, Paton DC, and Kuchel T. (1998) "Snake bites recorded by Veterinary Practices in Australia" *Aust Vet J* V76, No3: 195-198
- 5 Sutherland SK and Leonard RL. (1995) "Snakebite deaths in Australia 1992-1994 and a management update" *Med J Aust* 1995 163: 616-618
- 6 Kelloway CH (1931) "Observations on the certainly lethal dose of the venom of the common brown snake (*Dermansia textilis*) for the common laboratory animals" *Med J Aust* 2, 747-751
- 7 Tibballs J, Sutherland SK (1991) "The efficiency of antivenom in prevention of cardiovascular depression and coagulopathy induced by brown snake (*Pseudonaja*) species venom". *Anaesth Intens Care* 1991; 19:530-534
- 8 Sprivulis P, Jelinek GA and Marshall L (1996) "Efficiency and Potency of Antivenoms in Neutralising the Procoagulant Effects of Australian Snake Venoms in Dog and Human Plasma" *Anaesth Intens Care* 1996; 24:379-381
- 9 Whitaker AN, McKay DG (1969) "Induction of hypotension in Rhesus monkeys and rabbits by intravenous thrombin injection" *Lab Invest* 1969; 20:79-86
- 10 Lalloo DG, Trevett AJ, Nwokolo N, Laurenson IF, Naraqi S, Kevau I, Kemp MW, James R, Hooper L, David R, Theakston G, Warrel D "Electrocardiographic Abnormalities in patients bitten by taipans (*Oxyuranus scutellatus canni*) and other elapid snakes in Papua New Guinea" *Transactions of the Royal Society of Tropical Medicine and Hygiene.*

- 11 Karlson-Stiber C, Persson H, Heath A, Smith D, al-Abdulla IH, Sjostrom L. (1997) "First clinical experiences with specific sheep Fab fragments in snake bite. Report of a multicentre study of Viper. berus envenomation" *Journal Internal Medicine* 241 (1):53-58
- 12 Moisisidis A, James A, Smith H, Cox J (1995) "Snake envenomation in cats" CSL Technical Update No 008, 1/11/95 CSL Limited 45 Poplar Rd Parkville Victoria 3052 Australia
- 13 Mead HJ, Jelinek GA (1996) "Suspected snakebite in children: a study of 156 patients over 10 years". *Med J of Aust* 164(80): 467-70
- 14 Trevett AJ, Lalloo DG, Nwokolo NC, Theakston DG, Naraqı S, Warrel DA, (1995) "Venom detection kits in the management of snake bite in Central Province, Papua New Guinea." *Toxicon* 33(5):703-5
- 15 Connolly S, Trevett AJ, Nwokolo NC, Lalloo GD, Naraqı S, Mantle D, Schofield IS, Fawcet PR, Harris JB (1995) "Neuromuscular effects of Papuan Taipan snake venom" *Annals of Neurology* 38(6):916-20
- 16 Trevett AJ, Lalloo DG, Nwokolo NC, Naraqı S, Kevau IH, Theakston RD, Warrell D (1995) "Electrophysiological findings in patients envenomated following the bite of a Papuan taipan (*Oxyuranus scutellatus canni*)". *Transactions of the Royal Society of Tropical Medicine & Hygiene* 89 (4): 415-7
- 17 Lewis PF (1994) "Myotoxicity and nephrotoxicity of common tiger snake (*Notechis scutatus*) venom in the dog" *Aust Vet J* 71(5): 136-9
- 18 Lewis PF, (1978) "Snakebite in Animals in Australia" The University of Sydney Post-Graduate Committee in Veterinary Science Proceedings No 36 Fauna - Part B, 287-309
- 19 Holloway SA & Parry BW (1989) "Observations on blood coagulation after snake bite in dogs and cats" *AVJ* 66(11): 364-366
- 20 Best PR, (1982) "Snake envenomation" in The University of Sydney Post-Graduate Committee in Veterinary Science "Anaesthesia and Intensive Care" Proceedings No62: 455-465
- 21 Barr SC (1984) "Clinical features therapy and epidemiology of tiger snake bite in dogs and cats" *Aust Vet J* 61:208-212
- 22 Cogger HG (1978) "The identification of Australian snakes" in The University of Sydney Post-Graduate Committee in Veterinary Science "Fauna" Proc No 36: 567-582
- 23 Commonwealth Serum Laboratories (1989) "Treatment of Snake Bite in Australia and Papua New Guinea using Antivenom" Antivenom package insert