**Snake Envenomation**

Peter Best  
Greencross South Tamworth Animal Hospital  
88 Duri Rd Tamworth N.S.W.  
Australia  
Phone 02 67654244  
Email: stah@stah.net.au

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**Summary:**

Most deaths are the result of delayed, inadequate or inappropriate administration of antivenom  

Struan Sutherland 1980

What’s new in 2013?  

……Lots !!!
Australia is unfortunate in having many species of venomous creatures, both on land and in the sea, including:

- 38 terrestrial snakes and 23 sea snakes,
- 22 spiders, 4 ants, the honey bee, 3 wasps, 2 beetles(!), 6 scorpions, 2 caterpillars, centipedes, millipedes, mosquitoes, sandflies, thrips and other insects.
- The platypus and echidna both have venomous defence systems.

In the coastal waters there are 2 blue-ringed octopi, 7 jellyfish, cone shells, 2 stonefish, 21 other fishes including the flathead, the Port Jackson shark, 11 rays, starfish including the crown of thorns, corals, anemones, urchins, stinging sponges, marine worms, leeches, frogs and toads.

As far as snakes go, Australia is home to the ten most lethal in the world, and of the world's top 25 venomous snakes, Australia has 21. The diamond-backed rattlesnake is ranked number 25 in the world, with the Indian cobra and black mamba 12th and 13th respectively!

**Incidence of Snake bite in domestic animals**

- Survey of 10% Australian Vets - 106 replies
- Estimate 6240 snake bite cases seen by Vets annually Australia wide
- Rural areas account for most, 78%, urban areas 22%
- Rural areas cats 47% dogs 47%
- Urban areas cats 66% dogs 34%

Incidence of snake bite in domestic animals

- Species of snake varied with their geographic distribution
- Administration of antivenom significantly improves chance of survival
  - Dogs 75% vs 31% if untreated
  - Cats 91% vs 66% if untreated

Mirtschin PJ et al AVJ (1998); 76:195-198
Seasonal incidence of snake envenomation

South Tamworth Animal Hospital

Identification of the snake

South Tamworth Animal Hospital cases 1996-9:

- Identification achieved in 46/165 cases (28%)
- Method of identification:
  - Morphological exam 32 cases
  - CSL Snake venom detection kit 14 cases
    tested total 33 cases
    false negative 19/33 ie 58%
- Brown snakes 72%, black (Pseudechis) spp 13%
  tiger 4%, whip snakes 4%
According to the Cogger guide for identifying snakes, Eastern browns do not have any undivided sub-caudal scales.

Unfortunately there is variation in this morphology depending on the age of the snake. Adolescent eastern browns can have several undivided sub-caudals adjacent the anal plate, making this an unreliable guide to differentiating adolescent Eastern browns from adolescent Mulga (King Brown) snakes.
Adolescent *Pseudonaja textilis* (Eastern brown snake)

*Pseudechis australis* (Mulga or King brown snake)

Some of the subcaudals are undivided

Ref: Glen Shae “The distribution and identification of dangerously venomous Australian terrestrial snakes” AVJ 1999 Dec 77:791-798

**Tiger snake.** Note shape of the frontal plate and the relative size of the frontal (F) and temporolabial (TL) plate in the tiger snake

**Mulga snake**

**Eastern brown snake.** Note the fusion of the temporolabial and the sixth supralabial (SL6) in the Eastern brown snake
Mulga snake *pseudechis australis*

Juvenile browns display considerable colour dimorphism
Australian snake venoms

- Yield and potency
- Species of snake
- Species susceptibility
- Envenomation dose
- Venom composition

Eastern brown snake
(Pseudonaja textilis)

- Average venom yield P. textilis
  - S.Aust: 4.41mg
  - Gold Coast: 8.14mg
- Max venom yield: 67.2mg
- LD50: 0.041mg/kg
- Presynaptic neurotoxin textilotoxin (88kD): 3% of venom
  - LD50: 1ug/kg
- Prothrombin activators - 2 types (190kD): 30% of venom
  - LD50 < 0.1ug/kg

Ref: Glen Shae “The distribution and identification of dangerously venomous Australian terrestrial snakes” AVJ 1999 Dec 77:791-798
Struan Sutherland “Australian Animal Toxins” 1983
Mainland tiger snake
(Notechis scutatus)

- Av. venom yield 35mg
- Max. venom yield 189mg
- LD50 0.118mg/kg
- Numbers decreasing
- Pre-synaptic neurotoxin: notexin (13.5 kD) LD50 6ug/kg.
  Phospholipase action.
  Strong myotoxin - rhadomyolysis
- Prothrombin activator 6% of venom
- Myoglobinuria & direct renal toxin

Ref: Glen Shae "The distribution and identification of dangerously venomous Australian terrestrial snakes AVJ 1999 Dec 77:791-798
Struan Sutherland "Australian Animal Toxins" 1983

Clarence River (rough-scaled) snake
Tropidechis carinatus

- Av. venom yield 5.5mg
- Max. venom yield 9.8mg
- LD50 1.36mg/kg (S.C. dose mice)
  Sheep 1.2mg IV fatal, 12mg SC OK
- Fangs 5mm in 0.91m specimen
- RIA strongest cross reaction with Tiger snake venom and notexin.
  Strong procoagglutant action (dogs)
  Potent phospholipase
  Strong myotoxin - rhadomyolysis

Ref: Glen Shae "The distribution and identification of dangerously venomous Australian terrestrial snakes AVJ 1999 Dec 77:791-798
Struan Sutherland "Australian Animal Toxins" 1983
Red-bellied black snake
(*Pseudechis porphyriacus*)

- Av. venom yield 37mg
- Max. venom yield 94mg
- LD50 2.52mg/kg
- Pre-synaptic neurotoxin: pseudexin (16.5kD)
  - 25% of venom
  - phospholipase A activity
  - LD50 480ug/kg
- Venom components inc: haemolysins, cytotoxins (local reactions).

Ref: Glen Shae "The distribution and identification of dangerously venomous Australian terrestrial snakes AVJ 1999 Dec 77:791-798
Struan Sutherland "Australian Animal Toxins" 1983

Mulga (king brown) snake
(*Pseudechis australis*)

- Av. venom yield 180mg
- Max. venom yield 600mg
- The most prolific venom producer
- LD50 1.91mg/kg
- Main toxin is mulgotoxin 13.48kD)
  - Pure myotoxin
  - LD50 200ug/kg
- A member of the black snake family
- Confused with eastern browns

Ref: Glen Shae "The distribution and identification of dangerously venomous Australian terrestrial snakes AVJ 1999 Dec 77:791-798
Struan Sutherland "Australian Animal Toxins" 1983
A member of the black snake family, Collett’s black snake is found in central Queensland. It is dangerous, but quite beautiful.

**Burton’s legless lizard or snake-lizard**
Distributed through all of Australia except the southern tip of WA and southern Victoria and Tasmania.
It makes a characteristic sound

Not all bites are from venomous snakes
All snakes are not dangerous
Up to 50% of bites from snakes, no venom is injected by the snake
Many bites in which venom is injected by the snake fail either to penetrate the skin or deliver a lethal dose
**Amount of venom injected**

- multiple bites
- defensive bite vs milking for venom
  
  a defensive bite will deliver more venom than that obtained by milking


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**Amount of venom injected**

- multiple bites
- defensive bite vs milking for venom
- season
  
  There is a greater yield of venom in the spring, after the snake comes out of hibernation

Amount of venom injected

- multiple bites
- defensive bite vs milking for venom
- season
- size of the snake
  e.g. young brown snakes will deliver less venom than adults


Amount of venom injected

- multiple bites
- defensive bite vs milking for venom
- season
- size of the snake
- hunting experience & agility of “victim”

Amount of venom injected

- multiple bites
- defensive bite vs milking for venom
- season
- size of the snake
- hunting experience & agility of “victim”
- geographic differences within species
  
  P. textilis (S.A.) av venom yield 4.41gm
  P. textilis (Gold Coast) av venom yield 8.14gm


- NB Up to 50% bites are “dry” ie no venom injected

### Variable Species susceptibility to snake venoms

<table>
<thead>
<tr>
<th>species</th>
<th>brown snake lethal dose (mg/kg)</th>
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<tbody>
<tr>
<td>horse</td>
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<tr>
<td>sheep</td>
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<td>rabbit</td>
<td>0.2</td>
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<tr>
<td>monkey</td>
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</tr>
<tr>
<td>rat</td>
<td>0.6</td>
</tr>
<tr>
<td>mouse</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Kelloway 1931

Venom is a modified saliva, and the venom glands are in fact salivary glands.

Slide courtesy Australian Museum
Composition of snake venoms

- Low molecular weight substances. (pre-paralytic signs)
- Various enzymes: phospholipases, hyaluronidase, metalloproteinases, L amino oxidase etc.
- Coagulants: prothrombin activator, factor V activator
- Neurotoxins: presynaptic & postsynaptic
- Haemolysins
- Myolysins and cytotoxins

Preparalytic Signs

- Due to rapid diffusion of low molecular weight toxins from the bite site
- Occurrence of pre-paralytic signs (vomiting, initial collapse, salivation, mydriasis, trembling) almost invariably indicates that a potentially lethal dose of venom has been delivered
- May only last a few minutes and patient seems to recover
- Brown snake antivenom (and likely all the others) does not bind well to the low molecular weight protein components of venom
The neurotoxins

- Neurotoxins and coagglutinants are the most important component in all Australian elapid venoms (except the Mulga snake which has a strong myotoxin).
- Envenomated prey become paralysed and ultimately death usually ensues because of
  - ventilatory failure due to the action of neurotoxins, (although myotoxins will ultimately achieve the same effect)
  - Results of venom induced consumptive coagulopathy
- Both pre synaptic and post synaptic neurotoxins are present in venoms.

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. They interfere with the cycling of synaptic vesicles. Small microstructural alterations in the presynaptic membrane occur (so called omega shapes or “frustration vesicles”) can be demonstrated clearly with electromicroscopy. Example:

**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 in mice. 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
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: 2 post synaptic neurotoxins are found in tiger snake venom: 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.
- The exception is the postsynaptic neurotoxin, pseudonajatoxin in brown snake venom. It is unusual in that 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.

The neurotoxins

“Frustration vesicles” or Omega bodies (arrowed) are visible on electron microscopy and are due to the direct action of the presynaptic neurotoxins in snake venoms
Phospholipases

A phospholipase is an enzyme that hydrolyzes phospholipids into fatty acids and other lipophilic substances. There are four major classes, termed A, B, C and D, distinguished by the type of reaction which they catalyze:

- **Phospholipase A**
- **Phospholipase A1** - cleaves the SN-1 acyl chain.
- **Phospholipase A2** - cleaves the SN-2 acyl chain, releasing arachidonic acid.

Present in all species of venomous snakes. Interfere with the prey's cardiac system, mainly to lower the blood pressure. Phospholipase A2 causes haemolysis by lysing the phospholipid cell membranes of red blood cells.

Many of the Australian snake pre-synaptic neurotoxins have strong phospholipase activity.

Note that an enzyme that displays both PLA1 and PLA2 activities is called a Phospholipase B.


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Coagulants

Many of the Australian snakes venoms have coagulant activity:

- **High coagulant activity**: taipan, brown, tiger and mulga
- **Mild coagulopathy**: death adder & black snakes
- **Coagulopathy of unlikely clinical significance**: sea snake
- **Little coagulopathy unless severe envenomation occurs**: Clarence River snake, and the small eyed snake
Coagulants

- Human fatalities after snake bite (including deaths due to cerebral haemorrhage) have led to renewed interest in the pro-coagulant activity of snake venoms, especially brown, taipan and tiger snake venom. These toxins are prothrombin activators which convert prothrombin into thrombin, resulting in a consumptive coagulopathy.

- 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.

1988: Poor affinity of Antivenom for Procoagulants

- Of clinical importance is the observations by Masci et al 1988 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.
The Prothrombin Activators

2013: Antivenom removes circulating venom

- Brown snake envenomation in man
  - There was no difference in INR (prothrombin time), recovery or clinical outcome between patients receiving one or more than one vial of antivenom.
  - Free venom was not detected in 112/115 patients post-antivenom with only low concentrations (0.4 to 0.9 ng/ml) in three patients.
  - NB The median peak venom concentration in 118 envenomed patients was 1.6 ng/mL (Range: 0.15-210 ng/mL)
- Tiger snake envenomation in man
  - One vial of TSAV appears to be sufficient to bind all circulating venom.

Effects of tiger snake venom and prothrombin activator

- In dogs the effects of tiger snake venom and venom prothrombin activator are almost identical.
- Prothrombin activator constitutes 6% of tiger snake venom.
- Cardiovascular effects:
  - Systemic hypotension (dose related)
  - Low cardiac output
  - ECG suggests myocardial ischaemia
  - Pulmonary hypertension
  - Onset 3-5 mins after IV inj 1-30ug/kg venom or 0.3-5.0 ug/kg prothrombin activator (0.2 to 4.4% av venom dose)
  - Duration 30-40minutes


**Figure 2:** Effect of Notechis scutatus venom (10 μg/kg) on systemic arterial pressure. Values are mean and one standard deviation. n=5
Following intravenous infusion of tiger venom in dogs, there is rapid systemic arterial hypotension, pulmonary hypertension and decreases in stroke volume and cardiac output. Heart rate remained relatively unaffected.

<table>
<thead>
<tr>
<th></th>
<th>Before venom</th>
<th>5 minutes after venom</th>
<th>30 minutes after venom</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>115 (14)</td>
<td>98 (18)</td>
<td>102 (10)</td>
<td>0.21</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>105 (14)</td>
<td>48 (10)</td>
<td>94 (17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>4 (2)</td>
<td>5 (2)</td>
<td>4 (1)</td>
<td>0.55</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>13 (1)</td>
<td>24 (5)</td>
<td>19 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAOP (mmHg)</td>
<td>7 (1)</td>
<td>10 (2)</td>
<td>7 (0)</td>
<td>0.02</td>
</tr>
<tr>
<td>CO (ml/kg/min)</td>
<td>181 (42)</td>
<td>50 (17)</td>
<td>153 (25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SV (ml/kg)</td>
<td>1.58 (0.29)</td>
<td>0.50 (0.12)</td>
<td>1.51 (0.28)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SVR (dyn.s.cm⁻⁵.kg⁻¹)</td>
<td>46.2 (12.6)</td>
<td>76.2 (24.1)</td>
<td>48.9 (16.5)</td>
<td>0.018</td>
</tr>
<tr>
<td>PVR (dyn.s.cm⁻⁵.kg⁻¹)</td>
<td>2.8 (1.3)</td>
<td>25.8 (16.2)</td>
<td>6.4 (2.5)</td>
<td>0.008</td>
</tr>
</tbody>
</table>


**Figure 1:** Percentage decrease in systemic arterial pressure (SAP) and dose of *Notechis scutatus* venom.
**Figure 1:** Percentage decrease in systemic arterial pressure (SAP) and dose of *Notechis scutatus* prothrombin activator.

Tibballs J. Anaesth Intensive Care 1998; 26:536-547

Transoesophageal echocardiogram prior administration of Tiger Snake prothrombin activator.
Transoesophageal echocardiogram prior administration of Tiger Snake prothrombin activator

During infusion of tiger snake prothrombin activator
Arrows indicate thrombi (th) within chambers and adherent to atrioventricular valves

5 minutes after infusion of tiger snake prothrombin activator
Note: distension of right ventricle and right atrium

Tibballs J. Anaesth Intensive Care 1998; 26:536-547
Coagulation: the role of thrombin

Tissue factor pathway (extrinsic pathway) is the primary pathway for initiation of coagulation.

The main role of the tissue factor pathway is to generate a "thrombin burst," a process by which thrombin, the most important constituent of the coagulation cascade in terms of its feedback activation roles, is released very rapidly.

The final common pathway in coagulation involves prothrombin activation into thrombin whose primary role is the conversion of soluble fibrinogen into insoluble fibrin.

PT tests extrinsic and common pathway. APTT tests intrinsic and common pathway.
Venom Induced Consumptive Coagulopathy

- Important coagulation factors are activated by specific venom toxins, and as they become exhausted coagulopathy develops.
- Results from activation of the coagulation pathway by snake toxins including thrombin-like enzymes, prothrombin activators, and factor X, VIII &V activators.
- Causes rapid defibrination
- It's not DIC. The time course of VICC differs with rapid onset and resolution, and the mechanism of initiation of coagulation activation differs because thrombin generation in DIC is mediated by the tissue factor/factor VIIa pathway (Ibister Semin Thromb Hemost. 2010 Jun;36(4):444-51)
- P. textilis prothrombin activator is able to coagulate citrated plasma, warfarin plasma, & Factor V- and Factor X-deficient plasmas; to convert purified human prothrombin to thrombin. Calcium ions & phospholipids had little if any effect on the rates of coagulation of citrated plasma (Masci 1988)

Effects of tiger snake venom and prothrombin activator

Results of Venom induced consumptive coagulopathy (VICC):

- Pulmonary vascular obstruction
  - Thrombii in the heart (echocardiography)
  - Pulmonary thromboembolism (gross & histological)
- Biventricular failure
- Coronary ischaemia +/- direct cardiotoxin
Venom Induced Consumptive Coagulopathy in Man

Complete VICC
Characterized by near/total depletion of fibrinogen, FV and FVIII, with an INR and aPTT that exceeded the upper limits of detection, within 2 h of snakebite. Prothrombin levels never fell below 60% of normal, suggesting that the toxins were rapidly eliminated or inactivated and re-synthesis of clotting factors occurred irrespective of antivenom.

Partial VICC
caused limited depletion of fibrinogen and FV, and almost complete consumption of FVIII.

Onset
Onset of VICC was more rapid with brown snake (Pseudonaja spp.) venom, which contains a group C prothrombin activator toxin, compared with the tiger snake group, which contains a group D prothrombin activator toxin and requires human FVa formation.

Resolution
Resolution of VICC occurred within 24-36 h irrespective of snake type.

CONCLUSIONS:
These results suggest that Australasian elapid prothrombin activators have a potent but short duration of action. Antivenom is unlikely to be administered in time to prevent VICC.


Venom Induced Consumptive Coagulopathy can induce Thrombotic Microangiopathy

- Thrombotic microangiopathies are a rare group of disorders with features such as microangiopathic haemolytic anaemia, thrombocytopenia and renal failure
- Occur in 11% of brown snake envenomated human patients irrespective if complete or partial VICC
- Not associated with cardiovascular collapse in those patients with VICC
- One paper looked at ADAMTS13 levels (test for Thrombotic microangiopathy) which was normal in 2 cases of Tiger snake envenomation
- NB ADAMTS13 is a metalloprotease responsible for cleaving large multimers of von Willebrand factor (vWF) into smaller units.

**Venom Induced Consumptive Coagulopathy can induce Thrombotic Microangiopathy: Histopathological findings in dog and cat**

- Pathological evidence of procoagulant venom activity support previous suggestions that an initial thrombotic state occurs in envenomed patients
- formed thrombi present in the heart, lungs (small fibrillar aggregates and larger, discrete thrombi) and kidneys
- venom toxins are able to be localised to specific tissues, in this case, venom was detected in the lung, kidney and muscle tissues of clinically envenomed animals

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**Effects of tiger snake venom and prothrombin activator**

- Coagulation and haematological effects
  - elevated APTT and PT
  - decreased fibrinogen (0 to 0.7 gm/L)
  - thrombocytopenia sometimes (microangiopathy)
  - leukopenia (onset - minutes, resolved 40 mins)
  - all prevented by prior administration of heparin (not recommended treatment)
- Mechanism for CVS, coagulation & haematological effects: mostly due to the prothrombin activator
  - not due to the release of platelet activating factor, thromboxane A2, histamine or serotonin during the coagulation process
Laboratory findings in a 44 year old man envenomated by a brown snake. The tests reveal a Venom induced consumptive coagulopathy syndrome which is slowly reversed over time following the administration of multiple vials of brown antivenom.

<table>
<thead>
<tr>
<th>Hours after bite</th>
<th>Platelets (x 10^9/L)</th>
<th>INR</th>
<th>APTT (s)</th>
<th>Plasma fibrinogen (g/L)</th>
<th>Fibrinogen degradation products (μg/mL)</th>
<th>Serum creatinine (μmol/L)</th>
<th>ALT (UL)</th>
<th>Creatinine kinase (UC)</th>
<th>Troponin I (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference range</td>
<td>150-400</td>
<td>0.9-1.3</td>
<td>29.5-40.5</td>
<td>2.1-4.0</td>
<td>&lt; 0.4</td>
<td>60-165</td>
<td>&lt; 41</td>
<td>&lt; 150</td>
<td>&lt; 0.10</td>
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<td>02:15</td>
<td>33</td>
<td>&gt; 10</td>
<td>&gt; 100</td>
<td>&gt; 0.3</td>
<td>&gt; 20</td>
<td>100</td>
<td>113</td>
<td>140</td>
<td>&lt; 0.4</td>
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<tr>
<td>Treatment with 2 ampoules of polyvalent, 5 of brown snake and 2 of tiger snake antivenom</td>
<td>111</td>
<td>&gt; 10</td>
<td>&gt; 100</td>
<td>&gt; 0.3</td>
<td>&gt; 20</td>
<td>131</td>
<td>201</td>
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<td>05:50</td>
<td>214</td>
<td>&gt; 10</td>
<td>&gt; 100</td>
<td>&gt; 0.3</td>
<td>&gt; 20</td>
<td>133</td>
<td>277</td>
<td>269</td>
<td>2.8</td>
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<tr>
<td>Treatment with 5 ampoules of brown snake antivenom (infusion completed at 09:30)</td>
<td>151</td>
<td>&gt; 10</td>
<td>&gt; 100</td>
<td>&lt; 0.3</td>
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<td>82</td>
<td>151</td>
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<td>31.4</td>
<td>3</td>
<td>30</td>
<td>90</td>
<td>77</td>
<td>&lt; 0.4</td>
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</tr>
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</table>

Laboratory findings in a 44 year old man envenomated by a brown snake. The tests reveal a Venom induced consumptive coagulopathy syndrome which is slowly reversed over time following the administration of multiple vials of brown antivenom.

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**Procoagulants and Coagulants**

- **1998 (Masci & Mirtschin):**
  CSL antivenom does not easily reverse the coagulopathy that occurs in dogs and humans envenomated by brown snakes. The doses required are much higher than those required to neutralise the neurotoxins.

- **2012 for man (Ibister et al)**
  VICC runs 12-36 hours and appears self limiting. Antivenom does not appear to help VICC unless given early. FFP is controversial but useful in man. Antivenom still required for other toxicity.

  1-2 vials appears enough for all species of snake (Humans!).

Efficacy vs effectiveness

• It is important not to confuse the efficacy of antivenom, defined as its ability to bind and neutralise venom-mediated effects under ideal conditions, and the effectiveness of antivenom, defined as its ability to reverse or prevent envenoming in clinical cases.
• There are numerous potential reasons for antivenom failure in envenoming including
  – antivenom ineffectiveness
  – venom-mediated effects may be irreversible
  – Antivenom unable to reach the site of toxin-mediated injury
  – rapid of onset of venom-mediated effects

Ref: Toxicology. 2010 Feb 9;268(3):148-54. Antivenom efficacy or effectiveness: the Australian experience. Isbister GK.

VICC

• Mediated by activation of the coagulation cascade by prothrombin activators.
• Taipan and Brown venom contain group C prothrombin activators
• Tiger venom contains group D prothrombin activators.
• Only need to activate 15% of available prothrombin before fibrinogen levels are undetectable.
• INR (Prothrombin time ratio: patient PT compared to normal PT), APTT elevated. Fibrinogen low. D-Dimer elevated.

Ref: Dr Ben McKenzie, Emergency Physician
    Bendigo Health
Factor levels in VICC - man

Isbister GK, Scorgie FE, O’Leary A, Seldon M, Brown SGA Lincz LF.
Factor deficiencies in venom induced consumption coagulopathy resulting from Australian elapid envenomation: Australian Snakebite Project (ASP-10)
Journal Thrombosis and Haemostasis 2010 (8); 2504-2513.

Duration of VICC in man

- Duration of VICC is limited
- Appear to be inactivated by unclear mechanisms irrespective of antivenom dose

Isbister GK, Scorgie FE, O’Leary A, Seldon M, Brown SGA Lincz LF.
Factor deficiencies in venom induced consumption coagulopathy resulting from Australian elapid envenomation: Australian Snakebite Project (ASP-10)
Journal Thrombosis and Haemostasis 2010 (8); 2504-2513.

Table 1. Lowest (or highest) coagulation test or factor level results recorded for each patient during hospital admission. Data are presented as median and 2.5 to 97.5 percentiles.

<table>
<thead>
<tr>
<th>Test</th>
<th>New-envenomed</th>
<th>Partial VICC</th>
<th>Complete VICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>N = 8</td>
<td>N = 18</td>
<td>N = 122</td>
</tr>
<tr>
<td>Number of samples</td>
<td>n = 22</td>
<td>n = 108</td>
<td>n = 551</td>
</tr>
<tr>
<td>INR</td>
<td>1.1 (1 to 1.5)</td>
<td>1.7 (1.2 to 10)</td>
<td>&gt;12 (1.3 to &gt;12)</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>33 (31 to 36)</td>
<td>44 (36 to 140)</td>
<td>&gt;160 (30 to &gt;180)</td>
</tr>
<tr>
<td>Fibrinogen (g L⁻¹)</td>
<td>2.9 (1.7 to 3.6)</td>
<td>0.6 (0.1 to 1.5)</td>
<td>&lt;0.37 (&lt;0.2 to 2.3)</td>
</tr>
<tr>
<td>Factor II (%)</td>
<td>96 (78 to 123)</td>
<td>76 (28 to 95)</td>
<td>56 (0.1 to 97)</td>
</tr>
<tr>
<td>Factor V (%)</td>
<td>100 (74 to 142)</td>
<td>53 (14 to 91)</td>
<td>71 (0 to 119)</td>
</tr>
<tr>
<td>Factor VIII (%)</td>
<td>74 (60 to 145)</td>
<td>19.4 (3 to 82)</td>
<td>101 (0.4 to 118)</td>
</tr>
<tr>
<td>Factor VII (%)</td>
<td>133 (88 to 195)</td>
<td>86 (37 to 109)</td>
<td>91 (43 to 153)</td>
</tr>
<tr>
<td>Factor IX (%)</td>
<td>97 (71 to 124)</td>
<td>75 (40 to 115)</td>
<td>70 (19 to 140)</td>
</tr>
<tr>
<td>Factor X (%)</td>
<td>106 (92 to 157)</td>
<td>63 (44 to 94)</td>
<td>54 (37 to 117)</td>
</tr>
<tr>
<td>vWfAg (%)</td>
<td>105 (59 to 159)</td>
<td>93 (25 to 161)</td>
<td>156 (0 to 358)</td>
</tr>
<tr>
<td>D-dimer (mg L⁻¹)</td>
<td>0.38 (0.7 to 1.6)</td>
<td>140 (12 to 740)</td>
<td>836 (1.7 to 906)</td>
</tr>
</tbody>
</table>

INR, international normalized ratio; aPTT, activated partial thromboplastin time; vWfAg, von Willebrand factor antigen. *an INR of 12 was unrecordable for example > 12 and an aPTT of 180 was unrecordable for example > 180 s; †the limit of detection for fibrinogen is 0.2.
Venom Induced Consumptive Coagulopathy (VICC) in man

- Rapid onset.
- Clotting factors fall, fibrinogen consumed.
- Runs a course of 12 to 36 hours.
- Gets better as factors are resynthesized.
- Antivenom unlikely to help at all with VICC unless given early
- However antivenom likely plays a role in treating systemic, cardiac, neurological and muscle toxicity.
- Coagulopathy is not an end point to titrate antivenom therapy
- Bleeding is treated like any other bleeding coagulopathic patient.
- FFP without bleeding controversial.

Ref: Dr Ben McKenzie, Emergency Physician
Bendigo Health

Myolysins, cytotoxins and haemolysins
Myolysins & 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 two it is their main neurotoxin that is responsible of their venoms myotoxin action i.e 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.

Myolysins & cytotoxins

Papuan black snake, taipan, death adder and brown snake.

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).

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.

Lewis (1994) 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 emphasised the need for supportive treatment (IV fluids) aimed at maintaining renal function in envenomated dogs.
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 haemoglubinuria 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.

Antivenom

- History
  - The first antivenom was developed in horses in 1895 by French physician Albert Calmette for the treatment of Indian cobra bites (of BCG tuberculosis vaccine fame)
  - First Australian antivenom developed 1930 against tiger snake envenomation

- Potency
  - bioassay in guinea pigs
  - 1 unit neutralises 0.01mg venom

- Sources:
  - CSL: equine IgG Fab
  - AVSL: bloodhounds & sheep IgG Fab
  - Summerland: equine IgG purified

- Recommend dose
  - sufficient to neutralise the “average amount” of venom
  - 2x dose if symptoms of envenomation
  - often multiple vials required
Time for onset of clinical signs

- **Cats:** Bite to first signs. Range: minutes to 25 hrs
  - 21 hrs (Hill & Campbell 1978)
  - 15 hrs (Barr 1984)
  - 12 hrs (Holloway and May)

- **Dogs:** Bite to first signs. Range: minutes to 25 hrs
  - pre-paralytic signs 5-30 mins
  - tiger snake bite (Lewis 1994)
    - mydriasis 2-4 hrs
    - paralysis and death 2.5 to 5 hrs

- **Man:** Laboratory test (INR, aPTT and CK) & neurological reassessments identified nearly all severe envenoming cases within 12 hours of the bite. Although 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.

All patients suspected of envenomation should be observed closely for a minimum of 24 hrs.

**Diagnosis of Snake Envenomation**

- Each species of the 6 most venomous snakes produces a characteristic and specific envenomation syndrome in each of the domestic animal species and man.
- **Variations between 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).
  - Rhadomyolysis, myoglobinuria & renal failure (sea snake, mulga, tiger & taipan).
  - Renal toxicity (Tiger and black snake species).
  - Haemolytic venoms (all black snakes but especially red-bellied & copperhead).
  - Limb or facial swelling (black snake species).
Diagnosis of Snake Envenomation

- Diagnosis based on clinical signs alone remains unreliable.
  Pearn et al Toxicon 2000 Dec 38(12)1715-29
- 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
  Heller J, Mellor DJ et al AVJ 2007 Nov 85(11) 469-79

Clinical signs of snake envenomation

**cats**
Variable initial symptoms
Cats initially often show weakness & ataxia.
Other signs often inconsistent or transient:

- intermittent weak struggling
- lethargy
- tachypnoea
- dyspnœa
- haematuria
- plaintive vocalisation
- absent pupillary light reflex
- disorientation
- mydriasis
- posterior paresis
- generalised paresis
- often tail movement retained
- ataxia
- salivation
- bleeding from bite site
- coma
Goliath, a 3 year old cat suffering from a black snake envenomation.

Note the haematuria/myoglobinuria often found in cases of black snake envenomation.
This cat was envenomated with a black snake. Note the high CPK and AST.

<table>
<thead>
<tr>
<th>Routine</th>
<th>(Ref Range)</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>mmol/L</td>
<td>(134 - 143)</td>
<td>133 L</td>
</tr>
<tr>
<td>Potassium</td>
<td>mmol/L</td>
<td>(3.3 - 4.6)</td>
<td>7.3 H</td>
</tr>
<tr>
<td>Chloride</td>
<td>mmol/L</td>
<td>(102 - 112)</td>
<td>103</td>
</tr>
<tr>
<td>Bicarb.</td>
<td>mmol/L</td>
<td>(20 - 31)</td>
<td>19 L</td>
</tr>
<tr>
<td>Urea</td>
<td>mmol/L</td>
<td>(2.5 - 6.0)</td>
<td>15.5 H</td>
</tr>
<tr>
<td>Creatinine</td>
<td>umol/L</td>
<td>(40 - 70)</td>
<td>102 H</td>
</tr>
<tr>
<td>Anion Gap</td>
<td>mmol/L</td>
<td>(7 - 17)</td>
<td>18 H</td>
</tr>
<tr>
<td>Calcium</td>
<td>mmol/L</td>
<td>(2.19 - 2.64)</td>
<td>1.97 L</td>
</tr>
<tr>
<td>Phosphate</td>
<td>mmol/L</td>
<td>(1.05 - 1.80)</td>
<td>2.06 H</td>
</tr>
<tr>
<td>T-Protein</td>
<td>g/L</td>
<td>(59 - 78)</td>
<td>79 H</td>
</tr>
<tr>
<td>Albumin</td>
<td>g/L</td>
<td>&lt; 20</td>
<td>33</td>
</tr>
<tr>
<td>Calc.Glob.</td>
<td>g/L</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>umol/L</td>
<td>&lt; 20</td>
<td>9</td>
</tr>
<tr>
<td>GGT</td>
<td>U/L</td>
<td>(1 - 22)</td>
<td>2</td>
</tr>
<tr>
<td>Alk.Phos.</td>
<td>U/L</td>
<td>(88 - 315)</td>
<td>21</td>
</tr>
<tr>
<td>ALT</td>
<td>U/L</td>
<td>(1 - 20)</td>
<td>776 H</td>
</tr>
<tr>
<td>AST</td>
<td>U/L</td>
<td>(1 - 45)</td>
<td>8223 H</td>
</tr>
<tr>
<td>CK</td>
<td>U/L</td>
<td>(1 - 230)</td>
<td>&gt;99000 H</td>
</tr>
<tr>
<td>Glucose</td>
<td>mmol/L</td>
<td>(3.5 - 11.0)</td>
<td>20.6 H</td>
</tr>
<tr>
<td>Amylase</td>
<td>U/L</td>
<td>(20 - 125)</td>
<td>1300 H</td>
</tr>
<tr>
<td>Lipase</td>
<td>U/L</td>
<td>&lt; 190</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>mmol/L</td>
<td>&lt; 4.5</td>
<td>4.0</td>
</tr>
</tbody>
</table>

**Clinical signs of snake envenomation**

*dogs*

preparalytic signs
followed by apparent recovery lasting 30 to 120mins but *indicates a potentially lethal dose*
Pre-paralytic signs may include mydiasis, salivation, vomiting and temporary collapse.
Clinical signs of snake envenomation

dogs

diverse signs
sudden deterioration

• vomiting
• haematemesis
• haematoptysis
• trembling
• salivation
• excitement
• weakness
• mydriasis

• ptosis
• initial posterior paresis
• struggling
• tachypnoea
• shallow respiration
• flaccid paralysis
• coma

Clinical signs of snake envenomation

Often rapid progression to death

• procoagulant causing intravascular coagulation especially in RA, RV, pulmonary arteries
• decrease BP, cardiac output and SV. Increase PAP
• N-M junction blockade, flaccid LMN paralysis & respiratory failure
Time worsens envenomation

In envenomated patients that have had a long time lag between snakebite and treatment, there will be irreversible binding of pre-synaptic neurotoxin.

This means there is unlikely to be a good correlation between circulating levels of venom and antivenom and clinical events.

Holly
10yr old Fn

Mulga snake envenomation
Local bite site swelling
Pulmonary oedema
2 vials black antivenom
Ventilated 1.5hrs
SVDK +ive black snake
Successful resuscitation after cardiac arrest following massive brown snake envenomation. MJA 2002 (11) 646-649
Johnston MA, Fatovich D, Haig AD & Daly FS

This Doberman survived a brown snake envenomation, but treatment required 13 vials of 1000 unit CSL brown antivenom, 2 packs of whole blood, 1 pack of fresh frozen plasma and artificial ventilation for 36 hrs.
Note: The von Willebrand’s status of the dog was not known.
Treatment of snake envenomation

- Antivenom
- Prompt administration
- Adequate dose
- Appropriate antivenom

How much antivenom?
How much antivenom?

- One vial of CSL antivenom will neutralise in vitro the average venom yield.
- However, an envenomated animal may receive a dose that may vary considerably from average.
- Patients for whom treatment has been delayed may also require more than the initial recommended dose of antivenom.
- CSL states that if symptoms and signs of envenomation are already present, at least twice the recommended dose of antivenom should be infused.

How much antivenom?

Man vs Companion animals

- For man 1-2 vials is the current (2013) recommendation especially for brown snake envenomation. Neurotoxicity occurs <2% of patients and is mild. “Brown snake paradox”. Deaths are associated through VICC complications such as massive haemorrhage or cardiac arrest.
- Dogs and cats deaths are in part due to VICC complications but the most common cause is ventilatory failure, the signs produced by neurotoxins. Providing IPPV and administering repeated antivenom vials until the patient can maintain spontaneous ventilation saves most (>90%) of our severely envenomated patients (at least in our hands)


How much antivenom?

- Our experience. Often owner cost constraints mean some pets only receive 1-2 vials. These pets can and do frequently die.

Treatment of snake envenomation

Preferably dilute the antivenom at least in its own volume of saline and infuse slowly over 20 minutes, clinical situation permitting.
Treatment of snake envenomation

- IV catheter & fluids
- Pretreatments
  - antihistamine IV
  - Adrenaline 10 ug/kg SC
- Maintain normothermia

Anaphylactic and allergic reactions

- Antivenoms can bind complement and produce an anaphylactoid reaction in patients with no prior exposure to equine globulins, hence the recommendation for pre-treatments, dilution and slow administration
- In man pre-treatments has been shown not to change the incidence of allergic phenomena
- More reactions occur with tiger and polyvalent antivenoms (41%) vs brown snake (10%)
Immobilisation is an important part of first aid for both the human & domestic pet snakebite victim. Keeping an envenomated animal quiet delays the systemic absorption of venom and may help minimise myotoxic effects of tiger snake venom and the effects of procoagulant in brown and taipan venom.

**Treatment of snake envenomation**

**Cardiac rhythm disturbances**
- bradycardia
- ST segment depression or elevation
- AV block
- T wave depression
- Ventricular ectopia

**Treatment:**
- Antivenom
- Supplementary oxygen
- IPPV
- Atropine
Treatment of snake envenomation

Respiratory Support

- **Supplementary O2**
  - Nasal oxygen catheter
  - hypoventilation on room air always causes hypoxia
- **IPPV**
  - Warm & humidify
  - Inspired $O_2$ 40-60%
  - Dogs 15-20cmH$_2$O $ETCO_2$ 30-40mmHg
  - Cats 10-15cmH$_2$O $ETCO_2$ 20-30mmHg

Managing Intubation & IPPV

- Both envenomated dogs and cats can rapidly develop ventilatory failure. Some will struggle but are in fact not adequately ventilating (if using a face mask observe $ETCO_2$, or place two nasal $O_2$ catheters, one for $O_2$ administration the other for capnography gas sampling).
- Despite hypoventilation, the $ETCO_2$ is not always raised. One possible explanation for this is that VICC produces extensive pulmonary thromboembolism and thus marked V/Q abnormalities, substantially altering the lungs ability to eliminate CO$_2$
- Often the severely envenomated patient can be intubated without any resistance. But if it is necessary, may have to lightly anaesthetise the patient to achieve this, for instance Alfaxan 0.1 to 1.0mg/kg IV given slowly to effect
- Start IPPV. If necessary provide $\frac{1}{4}$% to $\frac{1}{2}$% Isoflurane to maintain intubation to prevent patient struggling against intubation and IPPV – at fractional MAC doses, cardiodepressant effects of Isoflurane are mild.
Managing IPPV and any additional antivenom requirements

• Once a regular ETCO₂ capnograph trace is obtained, every 10-30 mins test the patients ability to spontaneously ventilate by turning the ventilator off.
• If no spontaneous breathing returns,
  – administer another vial of antivenom and reinstitute IPPV
  – repeat this cycle until spontaneous ventilation returns
• If spontaneously ventilating normally for 5-10 mins,
  – turn the vaporiser off and extubate when consciousness returns.
  – Be prepared to re-intubate, as some patients do well spontaneously breathing whilst intubated but develop ventilatory failure once extubated.

Avoid Barotrauma

If ventilating a patient, one must be able to monitor the inspired pressures. Note the manometer located on the circle patient breathing system. Inspiratory pressure should not exceed 20cm H2O.

If using an anaesthetic ventilator, connect the ventilator to the patient breathing system in place of the reservoir bag. Ensure the exhaust (pop-off) valve is fully closed.
Avoid “volu-trauma”
The heterogenous nature of diseased and/or damaged lung means that some lung units have poor compliance and other are overly compliant. Large inspiratory volumes will result in uneven distribution of ventilation and may cause tearing of lung tissue. Permissive hypercapnia OK provided that the patient is not hypoxaemic

A patient ventilator can be made to ventilate the patient via an anaesthetic breathing system by using a “bag in the bottle” or simply by using a long tube - approx 10cm of a 22mm corrugated tube per kg weight as depicted in the image above

Ensure:
1. Patient Breathing System (circle system) exhaust valve is turned off
2. You must still provide fresh gas flow into the breathing system via rotameters (minimum of 40 ml/kg/min)
PEEP
(Positive End Expiratory Pressure)

Pulmonary oedema occasionally may arise during treatment of a snake envenomated case. IV fluids are routinely given at maintenance rates.

Treatment:
Initially administer 2-4mg/kg furosemide
If this does not resolve the problem, we have used low (5-6cm H₂O) PEEP to successfully resolve pulmonary oedema in envenomated patients

Avoid the use of 100% oxygen for periods longer than 8 hrs
Provide air-oxygen blended inspired gas for extended periods of IPPV
**Inspiratory pressures < 20cm H2O**

- To avoid excessive falls in cardiac output
- You must have a manometer

**Treatment of snake envenomation**

**Fresh Frozen plasma**

Replacement of clotting factors with fresh frozen plasma does not help brown snake envenomed dogs

- In 11 dogs given 1ug/kg brown snake venom, 30 min later brown antivenom, another 30 mins 2 units FFP or saline
- Of the six study dogs given antivenom plus FFP, two died at around 60 to 90 minutes post envenoming, at the end of the FFP infusions, and all but one of the survivors had persistent afibrinogenaemia.
- Of the five study dogs given antivenom and no FFP, all but one had return of detectable fibrinogen at eight hours after envenoming. None died
- Post mortem examinations of dogs that died during dosage and administration studies showed massive intracardiac clots

monitoring the ventilated patient

- observation of patient & ventilator
- capnography
monitoring the ventilated patient

- observation of patient & ventilator
- capnography
- pulse oximetry

- temperature
Clean endotracheal tubes every 4-6 hrs and change at least once every 24 hours in ventilated patients.

Note surprisingly rapid accumulation of mucous.

**Care for a ventilated patient:**

[www.stah.net.au](http://www.stah.net.au) go to tab “For Veterinarians”. Download spreadsheet.
**morbidity**

- delayed recovery
- bite site haematoma
- Thrombotic microangiopathy: renal failure, haemolytic anaemia, thrombocytopenia
- pyothorax
- myasthenia
- anaphalaxis to antivenom
- serum sickness days after antivenom

**Anti-venom adverse effects**

- Immediate reactions
  - 24% of humans
  - Usually not severe
  - Anaphalaxis (11% of humans)
- Serum Sickness
  - Type III hypersensitivity reaction
  - Immune complex deposition
  - Onset of symptoms 4-14 days post exposure
  - Fevers, rash and polyarthralgia/arthritis
  - Self limiting, treated with steroids
  - Unclear role of prophylactic steroids

Clinical Pathology

CSL snake venom detection kit

- Detect venom levels to 10ng/ml of sample
- Positive results in definitely envenomated patients
  - In man 28%, 85%, 35%
  - Companion animals (this review) 42%
- False negative test results are common in lethally envenomated animals
  - Venom concentration below detectible levels at the time sample was collected (too early, too late)
  - Time course of detectible concentration of venom in blood and urine
  - Other factors

This test is positive for an eastern brown snake
Concentration of brown snake venom in cat blood peaks at 1-2 hours undetectable at 24 hours.

Often urine is the preferred sample on which to perform CSL venom detection kit test since the bite sites are rarely identified in animals. As can be seen in the work of Moisidis et al there is a specific time dependant excretion profile for various venoms.

Concentration of brown snake venom in cat urine peaks at 4-24 hours undetectable by 28 to 40 hours.
Concentration of tiger snake venom in cat blood peaks at 1-2 hours none detected by 12 hours.

As opposed to brown snake venom, no detectible levels of venom are detectable in blood following tiger snake envenomation within 12 hrs.

Concentration of tiger snake venom in cat urine appears at 6-8 hrs, peaked at 16 hrs and then gradually declined to low levels by 24 hrs.
**CSL snake venom detection kit**

This is NOT a reliable test to exclude a diagnosis of snake envenomation

---

**Clinical Pathology**

- clotting times: PT, APTT, ACT.
- fibrinogen
- FDP, D-dimer test
- PCV & TPP
- urinalysis: Hb, Myoglobin, rbc, casts
- renal function: Urea, creatinine, K, urine s.g.
- enzymology: CPK, AST, LDH, myoglobin
- Full blood count esp platelet count, red cell fragments
Clinical Pathology

- ISTAT
  - Activated clotting time
  - blood gases, pH
  - blood urea, creatinine, electrolytes
  - Hct, Hb, glucose

Our treatment outcomes 1996-1999

- The analyses were performed using a generalised linear model
  - Overall, patients treated with antivenom 88% (92/104) were more likely to survive than those not so treated 69% (42/61) significant p=0.018
  - The interaction of patient species with treatment is marginally significant p =0.06. Stronger for dogs
  - Similar to figures from other authors
    - Barr 1984: Snake bite in 125 dogs and 115 cats over 10 years. Overall recovery rate after administering antivenene was 90% for cats and 83% for dogs
    - Hill 1979: Snake bite (mostly tiger) in 80 dogs over 7 years. 83% recovery with antivenom

Ref:
Our treatment outcomes 1996-1999

For all envenomated patients treated with antivenom: Survival where species of snake was known vs unknown:

- dogs:  
  known snake species 92% (22/24) vs  
  unknown 93% (14/15)
- cats:  
  by known snake species 92% (12/13) vs 
  unknown 82% 42/51

no significant differences

Our treatment outcomes 1996-1999

Survival of all seriously envenomated patients requiring mechanical ventilation where species of snake was known 83% (10/12) vs unknown 50% (5/10)

significant difference p = 0.043
Future developments

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 can be hard to differentiate on basis of clinical examination alone

- Correlations between securely identified species and the domestic animal envenomation syndromes have been slow to develop.

Ref: Toxicon 2000 Dec 38(12)1715-29 The envenomation syndrome caused by the Australian Red-bellied Black Snake Pseudechis porphyriacus. Pearn et al

Future developments

Each species of the 6 most venomous snakes produces a characteristic and specific envenomation syndrome in each of the domestic animal species and man

- Neuromuscular blockade (brown, taipan, copperhead, tiger, death adder)
- Coagulopathy (brown, taipan, tiger, mulga snake in dogs, death adder)
- Rhadomyolysis, 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)
Summary:

most deaths are the result of
delayed, inadequate or inappropriate administration of antivenom

Struan Sutherland 1980

Summary: Prompt, Adequate & Appropriate Antivenom Treatment

• Preparalytic signs = potentially lethal envenomation
• Be prepared for rapid deterioration
• Tx often requires multiple doses of antivenom
• Early Tx easier to reverse neuromuscular blockade
• Early Tx after pre-paralytic signs but before onset of serious envenomation may greatly decrease the dose of antivenom required.
• Mechanical Ventilation saves lives
• Long latency periods in cats and dogs (must observe suspect patients for 25hrs)
Summary: Prompt, Adequate & Appropriate Antivenom Treatment

- CSL venom detection kit - low sensitivity. False negatives common. Occasional false positive
- Prothrombin activator & intravascular coagulopathy responsible for many of the clinical signs in dog & man
- Old antivenom does retain considerable 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
- CSL monovalent antivenoms are often polyvalent but variable concentrations and affinities
- Antivenom cross reactivity is better for procoagglutants than neurotoxins

Summary: Prompt, Adequate & Appropriate Antivenom Treatment

- Venom Induced Consumptive Coagulopathy (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 and haemolytic anaemia)
- In humans the administration of Fresh Frozen plasma (FFP) decrease the time to recovery from VICC whereas in dogs FFP increases lethality in experimental dugite (brown) envenomation
- Successful resuscitation after cardiac arrest if prompt CPR and IV antivenom
- Antivenom dose and time of antivenom administration has no influence of time to recovery from VICC.
The End