



# Eastern brown snake (*Pseudonaja textilis*) envenomation in dogs and cats: Clinical signs, coagulation changes, brown snake venom antigen levels and treatment with a novel caprylic acid fractionated bivalent whole IgG equine antivenom



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## ABSTRACT

This report describes the diagnosis and treatment of 16 confirmed cases of snakebite from the Australian eastern brown snake (*Pseudonaja textilis*) in dogs and cats. The clinical signs, brown snake venom antigen concentrations, coagulation parameters, and treatment outcomes following administration of an experimental caprylic acid fractionated bivalent whole IgG antivenom are documented. A brown snake venom antigen specific sandwich ELISA was used to retrospectively quantify venom levels in serum and urine. The characteristic clinical signs of envenomation in all cases were neurotoxicity to a variable extent and coagulation disturbances. The median serum venom concentration at presentation was 122 ng/mL and ranged from 1.9 to 3607 ng/mL. The median urine venom concentration at presentation was 55 ng/mL and ranged from 3.3 to 2604 ng/mL. Mechanical ventilation was used to successfully support respiration in three severely paralysed cases for 1–30 h. In four cases where serum samples were available post-antivenom treatment, venom was no longer detectable. Coagulation parameters measured on citrated plasma samples collected prior to antivenom from each case were abnormally prolonged to variable degrees in all cases. Three cases (2 dogs; 1 cat) were euthanized within four hours of presentation for either cost based reasons (2) or poor prognosis (1). One dog developed massive and potentially fatal pulmonary haemorrhage and was euthanized. *In vitro* testing of the venom procoagulant neutralising efficacy of the experimental antivenom demonstrated it was 9.6–72 times more effective when compared to two other commercial veterinary antivenom products. This is the first detailed report of a case series of *P. textilis* envenomation in dogs and cats. The envenomation syndrome in dogs and cats differed to that reported humans, dominated by neurotoxicity and coagulopathy; unlike in humans, where coagulopathy is of primary clinical significance.

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## 1. Introduction

The Australian eastern brown snake (*Pseudonaja textilis*) is considered one of the most dangerous and venomous snakes in the world, with bites to domestic animals common (Padula et al., 2016). This snake is also responsible for the majority of snakebite cases in humans in Australia (Allen et al., 2012); however, the total number of envenomed humans per year is small (~10%) compared to

estimates for dogs and cats. A mailout survey of veterinarians in 1996 found that annually, approximately 6200 cases of snake envenomation are treated by Australian veterinarians and 76% of these were for brown snakes (Mirtschin et al., 1998). Another survey of veterinarians in New South Wales, Australia, found that 40.6% of snakebite cases were due to brown snakes (Heller et al., 2005). Despite the large number of cases diagnosed and treated by veterinarians, surprisingly, there has been no detailed description of the clinical syndrome, venom concentrations and response to various forms of treatment described in animals.

The lethal effect of *P. textilis* venom in the cat was first demonstrated over 90 years ago by the subcutaneous injection of

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graded doses of venom into ten cats (Kellaway, 1931). A dose of 0.5 mg/kg resulted in death within 90 min whilst 0.1 mg/kg caused hind limb paralysis in 20 h, with death occurring the following day (Kellaway, 1931). From this work, a dose of 0.1 mg/kg was deemed lethal to the cat; and, was comparatively similar in toxicity in the cat to tiger snake venom (*Notechis scutatus*) (Kellaway, 1929). Further studies on the effect of *P. textilis* in mice and guinea pigs found that guinea pigs required a four-fold lower dose per body-weight than mice; the lethal dose in mice was similar to the lethal dose in cats (Kellaway, 1931). More recent studies of the venom of *P. textilis* found that it was highly toxic to mice with an LD50 of 0.053 mg/kg (Broad et al., 1979). Controlled experimental envenomation by subcutaneous injection of domestic cats with 0.1–0.5 mg/kg doses of whole brown snake venom induced severe clinical signs in cats including paralysis within 24 h (Moisidis et al., 1996). A dose of 0.1 mg/kg was considered fatal, which resulted in a peak serum venom concentration of 50–100 ng/mL and urine 100 to 1000 ng/mL (Moisidis et al., 1996).

The brown snake (*Pseudonaja* sp.) family presently contains nine different species found on the Australian continent (Cogger, 2014). However, due to the geographical distribution of *P. textilis* overlapping primarily with the most populated areas of Australia, *P. textilis* is the principal species responsible for human and animal envenomation. *P. textilis* has wide distribution across the eastern half of Australia and is found from the lower Cape York Peninsula in Queensland to south-eastern South Australia; it is not found in Tasmania (Cogger, 2014). The snake is agile, nervous, fast moving and varies in colour with horizontal banding present in some young snakes tending to solid colour with increasing age. Typical length is 1.5–2 m. The snake is preferentially found in dry areas, avoiding the swamp wet areas typical for tiger and red-bellied black snakes.

This study was undertaken to describe the clinical syndrome of natural eastern brown snake envenomation in dogs and cats, quantify serum and urine venom antigen concentrations, and assess response to treatment with an experimental bivalent whole IgG caprylic acid fractionated antivenom.

## 2. Materials and methods

### 2.1. Diagnosis and treatment

All clinical cases were treated at a specialist veterinary referral hospital or the emergency after hours service in the same facility located in Brisbane, Queensland, Australia (Veterinary Specialist Services and Animal Emergency Service, Underwood, Qld). Critical cases requiring close monitoring or mechanical ventilation (MV) were admitted to the Pet Intensive Care Unit, Underwood, Qld. Cases were prospectively enrolled during 2016–2017 as either primary presentations or referrals from other veterinary practices. Cases were handled by multiple veterinarians and the following general procedures were performed.

Depending upon the animal's condition at the time of presentation a triage procedure was performed by a veterinarian. Cases were scored for gait and respiration at initial presentation using the following system. Gait Score: 0 = no clinical signs; 1 = mild paresis, able to ambulate; 2 = able to stand/sit unaided but can't walk; 3 = unable to stand but can maintain sternal recumbency; 4 = unable to maintain sternal recumbency. Respiratory Score: A = no compromise; B = mild increase in effort and or RR; C = moderate, RR < 16 or > 40, minimal excursions, abdominal component; D = dyspnoea, cyanosis, unsustainable respiratory pattern, respiratory arrest, imminent death.

In cases presenting with severe respiratory distress an intravenous catheter was placed and the animal was immediately intubated and positive pressure ventilation commenced (Fig. 4). A

sample of citrated plasma and serum was frozen within 4 h of collection prior to antivenom administration and at various time-points for different cases throughout the hospitalisation period. A clinical diagnosis of brown snake envenomation was made based on the history, presenting signs and a urine or serum snake venom detection kit (SVDK; Seqirus, Parkville, Australia) was used where appropriate in an attempt to confirm the diagnosis of snakebite.

Antivenom was used from a single production batch. Immediately prior to use it was diluted to a volume of between 20 and 50 mL depending upon recipient bodyweight, and infused intravenously either manually or via a syringe pump so that the total volume was received within 20 min. In some cases, where a rapid effect was desired, the antivenom was diluted and administered intravenously as a bolus in less than two minutes. All cases received supportive intravenous fluids; either, Hartmann's solution or a mixed electrolyte solution (Plasma-Lyte 148, Baxter, Australia) was given during the period of hospitalisation, potassium chloride was supplemented if indicated. In some cases, sedation was administered to the animal to reduce stress; butorphanol (0.1–0.2 mg/kg; iv) initially, followed by a constant rate infusion (0.02–0.1 mg/kg/hour). Following antivenom administration, envenomed animals were monitored either intermittently or continuously depending upon clinical severity for mucous membrane colour, respiratory rate and effort, heart rate, blood pressure, blood oxygen saturation (SpO<sub>2</sub>) and rectal temperature. In cases where the respiratory rate and effort were deemed abnormal, venous blood gas measurements were performed for venous blood carbon dioxide tension (PvCO<sub>2</sub>).

During the period of hospitalisation, intensive nursing care was provided including soft bedding, sternal positioning with change from left to right every 2–4 h, eye care every 1–4 h case dependant, and application of protective contact lenses in mechanically ventilated or severely paralysed patients. Urine output was measured 4 hourly if the patient required an indwelling urinary catheter. Clinical chemistry tests were performed using in-house test equipment (VetScan2, REM Systems, Australia) or an external veterinary diagnostic laboratory (QML, Brisbane, Australia). Packed cell volume measurements were made using a centrifuge and micro-haematocrit tubes. Total plasma protein was measured using a handheld refractometer. Whole blood activated clotting time (ACT) was performed by collecting 2 mL of whole blood and rapidly transferring it to a commercial ACT tube (Actalyke, Helena Laboratories, Mt Waverly, Australia). The tube was immediately placed into a single well whole blood coagulation monitoring instrument designed to accurately measure ACT in seconds (Hemochron 401, Edison, New Jersey) The maximum clotting time for blood collected from normal healthy dogs and cats was 85 s (See et al., 2009).

MV was performed according to the Pet Intensive Care Unit protocol using total intravenous anaesthesia (TIVA). MV was recommended as an essential treatment if any of the following criteria were met: (i) hypoxaemia, defined as PaO<sub>2</sub> <60 mmHg or pulse oximetry (SPO<sub>2</sub>) values < 90% despite supplemental oxygen therapy; (ii) hypoventilation, defined by partial pressure of carbon dioxide in venous blood (PCO<sub>2</sub>) >60 mm Hg; (iii) respiratory arrest (cessation of thoracic excursions); or, (iv) unsustainable respiratory effort was observed and respiratory arrest appeared imminent.

To initiate MV, patients were anaesthetised using an intravenous bolus injection of alfaxalone (2–5 mg/kg; Alfaxan, Jurox, Australia) to enable orotracheal intubation. Patients were maintained on TIVA to provide a light plane of anaesthesia and provide analgesia. All patients received a combination of butorphanol (0.1–0.2 mg/kg/h; Ilium Butorgesic Injection, Troy Laboratories, Australia) and midazolam (0.1–0.5 mg/kg/h; Midazolam Sandoz, Sandoz, Australia). Dogs received propofol (0.05–0.4 mg/kg/min) and cats received alfaxalone (1–4 mg/kg/h) administered by

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