Q J Med 1996; **89**:25–35

Neurotoxicity, anticoagulant activity and evidence of rhabdomyolysis in patients bitten by death adders (*Acanthophis sp.*) in southern Papua New Guinea

D.G. LALLOO[1,2], A.J. TREVETT[1,2], J. BLACK[1], J. MAPAO[1], A. SAWERI[1], S. NARAQI[1], D. OWENS[3], A.S. KAMIGUTI[4], R.A. HUTTON[3], R.D.G. THEAKSTON[5] and D.A. WARRELL[2]

From the [1]Department of Clinical Sciences, University of Papua New Guinea, Port Moresby, Papua New Guinea, the [2]Centre for Tropical Medicine, University of Oxford, the [3]Katherine Dormandy Haemophilia Centre, Royal Free Hospital, London, [4]Department of Haematology, University of Liverpool, and the [5]Alistair Reid Venom Research Unit, Liverpool School of Tropical Medicine, UK

Received 10 July 1995; Accepted 24 August 1995

Summary

Thirty-two patients with enzyme-immunoassay-proven death adder (*Acanthophis sp.*) bites were studied in Port Moresby, Papua New Guinea. Eighteen were envenomed; local signs were rare and none had incoagulable blood, but all except one had signs of neurotoxicity. Five (27.7%) envenomed patients required intubation and ventilation. One patient developed renal failure, previously undescribed following death adder bites. Laboratory investigations showed mild prolongation of prothrombin and partial thromboplastin times in some patients. *In vitro* studies showed that the venom contains anticoagulant activity, but does not cause fibrinogenolysis. In contrast to taipan envenoming, neurotoxicity did not progress after antivenom administration, and there was reversal of neurotoxicity, evident within 6 h, in three severely envenomed patients treated less than 12 h after the bite. One patient treated with antivenom and anticholinesterases had the most dramatic response to treatment; the optimum management of bites by this species may include prompt treatment with both antivenom and anticholinesterases in addition to effective first aid.

Introduction

The death adder (*Acanthophis sp.*) (Figures 1 and 2) is the most widely distributed venomous snake in Papua New Guinea (PNG). It is found throughout the mainland coastal regions of PNG and Irian Jaya, and at altitudes of up to 4000 ft in the Highlands. Death adders also occur throughout much of Australia and a number of eastern Indonesian islands (Figure 3). The relationship of PNG death adders to Australian species is uncertain; originally designated as '*Acanthophis antarcticus*', it now seems likely that *Acanthophis praelongus* and at least one other species exists in PNG.[1] Early work by Kellaway demonstrated a curare-like activity of the venom in rabbits and cats.[2] Subsequently, a number of venom components have been characterized, including four distinct neurotoxins which cause post-synaptic blockade *in vitro*.[3–6] The action of the venom on the coagulation system is less clear; anticoagulant, weak pro-coagulant and no pro-coagulant or anti-coagulant activity have all been described.[7–12] Fibrinolytic activity has not been demonstrated.[9] Australian case reports and a series reported by

Address correspondence to Dr D. Lalloo, Centre for Tropical Medicine, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford OX3 9DU

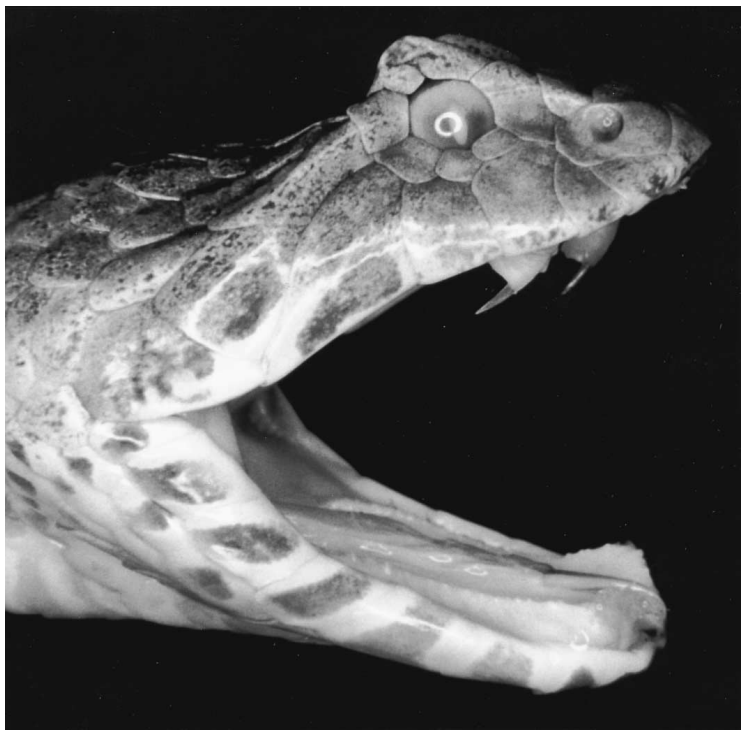

Figure 1. Detail of the head of a Papua New Guinean death adder (*Acanthophis sp.*) showing long fangs.

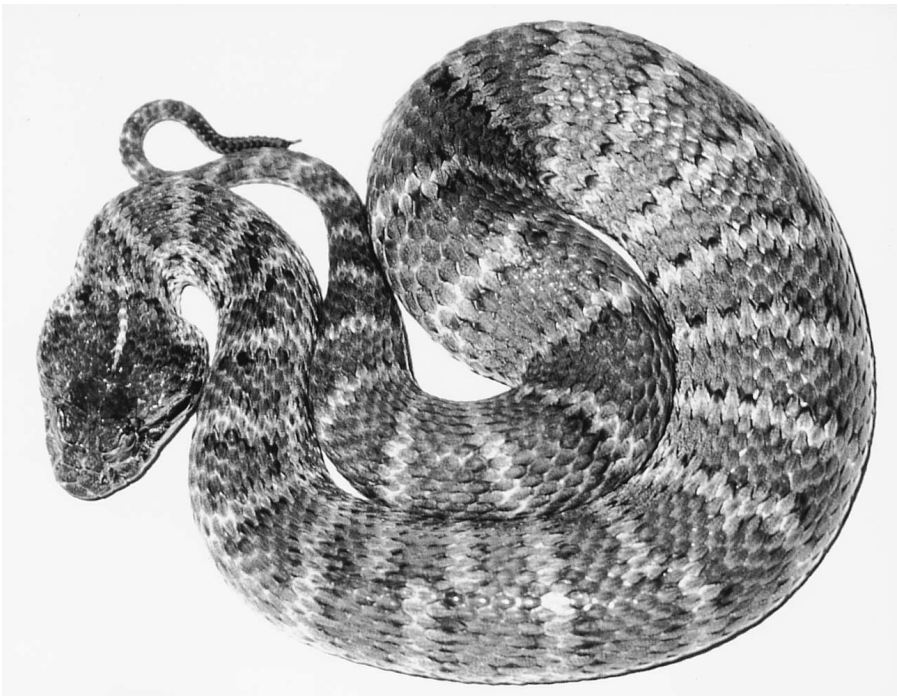

Figure 2. Death adder (*Acanthophis sp.*): live specimen 60 cm long from Goldie River, Central Province, Papau New Guinea.

Campbell from Port Moresby have demonstrated that the major effect of envenoming in man is neurotoxicity, which is sometimes dramatically responsive to antivenom.[13,14] We describe 32 envenomed patients with enzyme-immunoassay-proven death-adder bites studied over a two-year period.

Methods

All patients presenting with a history of snakebite to Port Moresby General Hospital (PMGH) between March 1990 and June 1992 were studied prospectively. History and examination were recorded on

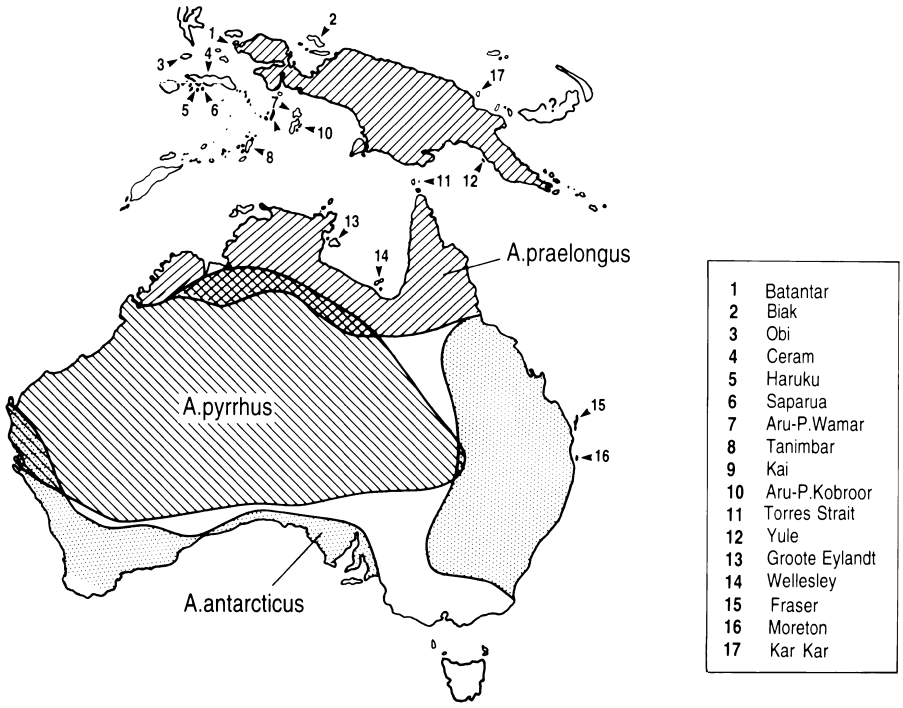

Figure 3. Distribution of death adders (genus *Acanthophis*).

standard forms. Blood was taken for haematological and biochemical investigations and 2 ml of whole blood was placed in a new, clean, dry, glass tube for determination of the 20 min whole blood clotting test (20 WBCT).[15,16] Blood (9 ml) was added to 1 ml tri-sodium citrate (3.8%), immediately centrifuged, separated and frozen in 1.5 ml aliquots at -70 °C for measurement of clotting factors, which were assayed as previously described.[17] Serum and urine samples, and bite wound swabs and aspirates were frozen at -70 °C for venom detection. Urine was examined by microscopy and tested by dipstick.

Patients with signs of envenoming (lymph node tenderness or neurotoxicity) were treated with one ampoule of polyspecific antivenom (Commonwealth Serum Laboratories, Melbourne) diluted to a total volume of 100 ml and infused intravenously over 20 min. Promethazine (12.5 or 25 mg intravenously) was given before antivenom as prophylaxis against reactions. Patients were examined at least six-hourly for the first 36 h and daily thereafter.

Venom detection

Samples were tested with antisera against the venoms of the five important species of venomous snake found in PNG: taipan (*Oxyuranus scutellatus canni*), Papuan black snake (*Pseudechis papuanus*), death adder (*Acanthophis sp.*), common brown snake (*Pseudonaja textilis*) and New Guinean small-eyed snake (*Micropechis ikaheka*) in an enzyme immunoassay (EIA).[18–20] Background absorbence was established by assaying 105 control samples from Papua New Guineans who had never been bitten by snakes. Death adder bite was diagnosed when a significant concentration (greater than mean + 2SD of control OD values) of *Acanthophis sp.* venom antigen alone was detected in one or more of the samples from each patient.

Effects of *Acanthophis sp.* venom on blood coagulation.

Increasing amounts of pooled Papua New Guinea death adder venom from Central Province, Madang and Karkar Island (1.25–20 μg) were added to 1 ml whole human blood in glass tubes. Tubes were incubated at 37 °C, and clot formation was observed at 1 min intervals. Venom was added to human plasma at increasing concentrations (1.25–10 μg/ml) and the prothrombin time (PT) and activated partial thromboplastin time (APTT) of the mixtures were recorded. Fibrinogenase (fibrinogenolytic) activity was investigated by the addition of venom (2.5–20 μg/ml) to a 2 mg/ml human fibrinogen (Kabi) solution. The mixture was incubated for 37 °C for 15 min, the reaction stopped with 5 mM EDTA, and the mixture analysed by SDS-PAGE in a 12% gel under reducing conditions.[21]

Statistical methods

Platelet counts and clotting factor measurements were compared between patients and controls using

t tests. Paired t tests were used to assess changes within individuals after antivenom. Two-tailed tests were used throughout and a significance level of 0.05 assumed.

Results

Clinical observations

Thirty-two patients (25 males) with a mean age of 25.9 (range 7–50) years were studied; 30 were from Central Province or the National Capital District and two were bitten in Western Province. Twenty-two (68.8%) were bitten during daylight hours and all but two were bitten on the lower limb. Two patients killed the snake; in one case this was brought to hospital and identified as a death adder. Central Province patients reached hospital between 1.75 and 43 (median 11.5) h after the bite; four had been referred from peripheral health centres.

Eighteen patients had signs of envenoming. Lymph node pain and drooping of the eyelids were the most common symptoms on admission; one patient complained of transient bleeding from the mouth, although this was not confirmed by clinical examination (Table 1). Symptoms were reported as early as 5 min after the bite; neurological symptoms were experienced between 1 and 13 (median 3.5) h after the bite. Neither local swelling nor other signs were seen at the bite site. Seventeen patients (94.4%) had neurotoxicity; signs were present by the time of admission in all (Table 2). The severity of neurotoxicity varied from mild ptosis to complete respiratory paralysis requiring ventilation (Figure 4). Progression of neurotoxicity could be rapid; one patient presented with a respiratory arrest 2 h after the bite and needed immediate intubation. Five patients (27.7%) required intubation and ventilation at a median time of 13 h (range 2–23.5) after the bite. Bleeding was not observed in any patient on admission, and all had normally clotting blood using the 20WBCT. All patients survived.

Thirteen patients were treated with antivenom; two received more than one ampoule, because of initial inappropriate treatment with taipan antivenom in one and uncertainty about the biting species in the other. One patient was treated with edrophonium as a diagnostic test and another was treated with neostigmine in addition to antivenom. The response to antivenom could be assessed in six patients treated between 3 and 43 h after the bite. In three patients treated 3, 4 and 12 h after the bite, there was a discernible response to antivenom compared with non-treated patients and patients bitten by other species. One patient who presented with complete ptosis, complete ophthalmoplegia and a respiratory arrest, had only mild ptosis within 18 h of antivenom and was ventilated for only 16 h. A second patient who required intubation on admission demonstrated an improvement in both peripheral weakness and respiratory muscle power during the administration of antivenom; signs of ptosis, ophthalmoplegia, restricted mouth opening and severe bulbar weakness had almost disappeared within 18 h after antivenom and the patient was intubated for only 4 h. The response was even more dramatic in a third patient treated simultaneously with antivenom, and intravenous neostigmine 0.45 mg and atropine 0.6 mg. Within 2 h of treatment, there was a marked improvement in respiratory effort and the patient could be extubated. Fourteen hours after antivenom, the

Table 1 Symptoms in 18 patients with evidence of envenoming by death adders*

General symptoms	No of patients with symptom	Frequency (%)
Lymph node pain	12	70.6
Headache	10	58.8
Drowsiness	9	52.9
Abdominal pain	8	47.1
Vomiting	5	29.4
Collapse	2	11.8
Bleeding from the mouth	1	5.9

Neurological symptoms	No of patients with symptom	Frequency (%)
Ptosis	15	88.2
Dysarthria	6	37.5
Dysphagia	5	29.4
Difficulty in breathing	3	20.0
Diplopia	3	18.8

* A clear history could not be elicited from every patient.

Table 2 Signs in 18 patients with evidence of envenoming by death adders*

Sign	No of patients with sign (%)
Swelling at bite site	0
Tender enlarged lymph nodes	11 (61.1)
Abdominal tenderness	6 (33.3)
Bleeding	0
Ptosis	17 (94.4)
Ophthalmoplegia	10 (55.6)
Diminished hand grip	5 (31.3)
Slurred speech*	4 (30.8)
Jaw restriction*	2 (28.6)
Diminished reflexes	2 (12.5)
Required intubation	5 (27.8)
Required ventilation	5 (27.8)

* Not assessed in every patient.

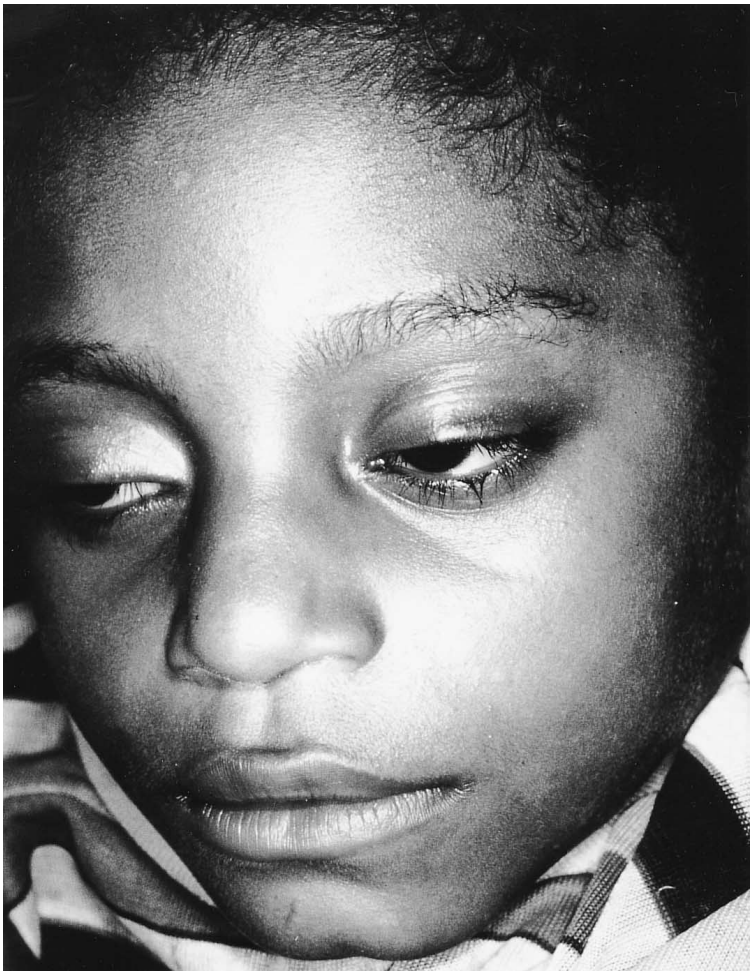

Figure 4. Ptosis in a 5-year-old girl bitten 4 h previously by a death adder at Baitarata, Madang Province, Papau New Guinea.

ophthalmoplegia, bulbar weakness and severe ptosis had resolved. Three other patients treated 18, 24 and 43 h after the bite showed no obvious response to antivenom; a complete ophthalmoplegia persisted for almost 48 h after antivenom in one and another required intubation for 70 h and had ptosis and an ophthalmoplegia which persisted for 72 h after antivenom. The response of neurotoxicity to antivenom could not be assessed in seven other treated patients, because of only mild neurotoxicity in three, initial treatment at health centres in two, delayed diagnosis in one child and inadequate follow-up observations in one patient.

Five patients did not receive antivenom; treatment was withheld in three patients with minor neurological signs and two patients presented late with stable neurotoxic signs. One who presented with marked ptosis and a partial ophthalmoplegia 18 h after the bite had normal eye movements and only mild ptosis 36 h after the bite. The other had ptosis and partial ophthalmoplegia which persisted for over 72 h after the bite.

Complications were rare. One patient developed pulmonary consolidation, probably secondary to aspiration. Another was referred from Western Province 5 days after the bite because of renal failure; the patient had a creatinine level of 1790 μmol/l on admission but was not fluid-overloaded or hypercatabolic. There was no clinical indication of serum sickness. Renal function recovered fully with conservative treatment. An electrocardiogram demonstrated second-degree atrioventricular block with a ventricular rate of 36 bpm which persisted throughout recovery. Although this rhythm could have pre-dated the snakebite, the observation of a pulse rate of 100 bpm on admission to the peripheral hospital suggests that the dysrhythmia was caused by the snakebite.

Illustrative case reports

Patient S1492

A seven-year-old girl was bitten on the right instep by a 34-cm-long death adder (Figure 5) close to a stream where she had been drinking. The snake was killed, and she was taken to a local health centre where a compression bandage was applied. When

Figure 5. Death adder (34 cm long) responsible for envenoming patient S1492 (Case report 1) at Ningerum, Western Province, Papua New Guinea.

she arrived at the hospital, 3.5 h after the bite, she was complaining of pain in the right groin and had been vomiting. Symptoms of neurotoxicity, heavy eyelids and difficulty in swallowing, had started about an hour and a half after the bite and she was beginning to have difficulty in breathing. On examination, there was tenderness but no swelling over two fang marks and she had tender lymph nodes in the groin. She had moderate ptosis, a partial ophthalmoplegia, and had developed pooling of secretions because of difficulty in swallowing. Respiratory efforts were weak and involved the diaphragm only. The whole blood clotting time was normal. She was immediately intubated and ventilated by hand. One ampoule of death adder antivenom was infused over 20 min, and she was given 0.45 mg neostigmine and 0.6 mg atropine intravenously. Over the following 2 h, there was a distinct improvement in the level of respiratory effort and the patient was extubated. Mild ptosis persisted, but 14 h after admission to hospital, all signs of neurotoxicity had disappeared and the patient made an uneventful recovery.

Patient 0492

A 30-year-old man was bitten by an unseen snake on the right foot whilst urinating at night close to his house. On waking, he had noticed slight pain in his foot, right groin and abdomen and had vomited. He had also noted slurring of speech and drooping of his eyelids. On arrival at hospital 12 h after the bite, two small fang marks were visible and he had tender enlarged lymph nodes in the groin. He had moderate ptosis, an almost complete ophthalmoplegia, marked dysarthria and jaw opening was restricted (interdental distance 12 mm). His breathing was very shallow and he was unable to swallow his secretions. The whole blood clotting test was normal. Intravenous edrophonium (10 mg) and atropine (0.6 mg) were given and there was a transient increase in the duration of upward gaze from 5 to 15 s five minutes later. One ampoule of death adder antivenom was infused intravenously and the patient was intubated. Within 30 min of antivenom, there appeared to be an improvement in the strength of his respiration, and there was a marked improvement in peripheral grip strength. The patient was able to extubate himself. Six hours after antivenom, he was breathing adequately spontaneously, but still had marked ptosis and an almost complete ophthalmoplegia. Eighteen hours after antivenom, there was very mild ptosis, but no other evidence of neurotoxicity; interdental distance was now 40 mm. The patient made a full and uneventful recovery.

Laboratory studies

Fourteen patients had laboratory investigations. The mean admission haemoglobin level was 12.5 g/dl.

White cell counts were slightly elevated in two patients on admission, and rose in three patients to peak counts of 16.5, 16.8 and 22.5×10^6/l in the absence of any other obvious cause. The mean admission platelet count (prior to antivenom) of 135.8×10^9/l was significantly reduced compared to controls (difference between means 89.9×10^9/l, 95% CIs for difference 44.7–135×10^9/l, $p = 0.0001$); platelet counts remained low for several days. Urea and electrolyte levels were normal in all but the one patient mentioned above. Creatine kinase (CK) levels were significantly elevated (prior to any intramuscular injection) in 8/12 patients on admission (median 411, range 164–4220 IU/l) and rose further in most patients during admission (median peak 548 IU/l).

Blood coagulation studies were done on admission in 13 patients (Table 3). When compared with 39 healthy Papua New Guinean controls, mean prothrombin time was significantly prolonged (16.2 vs. 14.4 s, $p = 0.0005$), but there was no difference in PTTK or fibrinogen levels. However, in six patients in whom repeated measurements were made between 36 h and 13 days after antivenom, there were significant reductions in PT and PTTK ($p = 0.0006$ and $p = 0.036$, respectively) and a non-significant elevation in fibrinogen levels ($p = 0.17$) after treatment. Clotting factor levels measured in one patient did not demonstrate a marked depletion in any of the coagulation factors or inhibitors (Table 4).

The addition of *Acanthophis sp.* venom to whole human blood prevented clot formation at levels in excess of 5 μg/ml. The venom had no coagulant effect on plasma. Both PT and APTT were prolonged in the presence of venom at a concentration of 1.25 μg/ml, although mixtures continued to clot up to the maximum venom concentration tested (10 μg/ml). No fibrinogenolytic activity could be demonstrated (Figure 6).

Venom antigen detection

Venom antigen was detected in the serum of 16 envenomed patients (88.8%) in concentrations from 7.8 to 5000 (median 48) ng/ml; the diagnosis was made by detection in the urine and in a wound swab in two patients. Three of 9 (33.3%) urines examined were positive for venom antigen; all three aspirates tested and two of six swabs tested were positive. Serum levels in 14 patients with no clinical evidence of envenoming ranged from 10 to 420 (median 24) ng/ml.

Discussion

The death adder is the second most common cause of envenoming in the Central Province and National Capital District of PNG, accounting for approximately

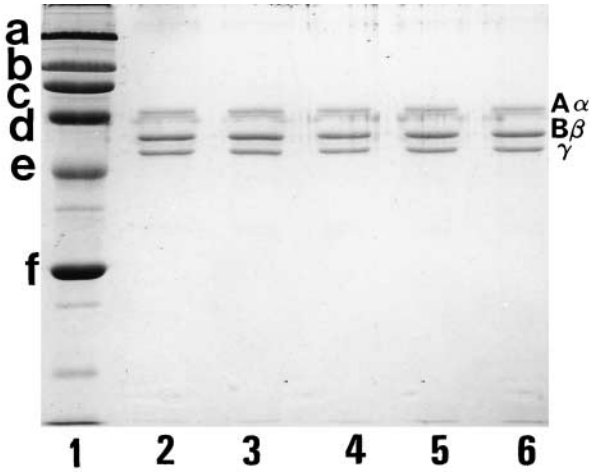

Figure 6. SDS-PAGE of fibrogen treated with *Acanthophis sp.* venom. Lane 2, control; Lane 3, 2.5 μg/ml venom; Lane 4, 5.0 μg/ml venom; Lane 5, 10 μg/ml venom; Lane 6, 20 μg/ml venom; Lane 1, molecular mass markers (a = 205 kDa, b = 116 kDa, c = 94.7 kDa, d = 66 kDa, f = 29 kDa). Reduced chains of fibrinogen are indicated (Aa Bb g). The gel was stained with Comassie Blue.

11% of envenomed patients presenting to hospital.[20] Although it is primarily nocturnal, we, like Campbell, found that many victims were not bitten at night; this may be the result of snakes sleeping on warm paths during the day.[13,22] Immunoassay data in envenomed and non-envenomed patients (not shown) suggest that envenoming is less common after death adder bites than after bites by the more common taipan; the 50% mortality rate in untreated death adder bites that was quoted in the early part of this century was clearly an overestimate.[23] The death adder appears to cause less severe envenoming than the taipan. Campbell described 15 cases bitten by death adders, eight identified by the dead snake and the rest by his patients' description of the snake.[13] Only three of these patients demonstrated neurotoxic signs, seven had tender lymphadenopathy alone and five were not envenomed. In our envenomed patients, signs of neurotoxicity were found in all but one, but these were usually mild. Only five patients (27.1%) developed severe neurotoxicity requiring intubation; in contrast 41.7% of taipan victims seen over the same period required intubation.[24]

The clinical picture of neurotoxicity was similar to that described in envenoming by other Australasian elapids.[25] However, the administration of antivenom appeared to be much more effective than in patients bitten by taipans and Papuan black snakes.[20,24] Neurotoxicity did not progress after antivenom in any patient, in contrast to the progression which occurs in 37% of patients bitten by the taipan.[24] None of the five patients who required intubation had been treated previously with anti-

Table 3 Blood coagulation studies in 12 patients bitten by death adders

Study number	Admission					Discharge		
	PT (s)	PTTK (s)	Fibrinogen (g/l)	Platelet count ($\times 10^9$/l)	FDP (μg/ml)	PT (s)	PTTK (s)	Fibrinogen (g/l)
s0590	15.9	43.2	3.25	—	—	13.9	42.7	5.41
s1990	14.1	46.9	2.18	116	—			
s3590	18.3	46.7	2.14	—	—	15.5	37.1	3.67
s4990	15.0	42.3	2.86	60	—			
s6890	18.3	44.7	1.81	183	<10			
s7690	16.3	45.2	1.56	64	20	15.0	44.9	1.79
s2491	16.3	38.9	3.49	—	—			
s2891	15.1	44.2	2.7	212	—			
s4091	15.6	38.9	2.98	—	—	13.8	36.2	1.93
s6491***	15.8	38.4	1.24	214	80	14.4	31.9	3.35
s7491	15.8	37.7	3.31	—	<10	14.4	30.2	3.34
s8491	16.6	41.2	3.56	—	<10			
s0492	19.2	45.2	2.28	73	—			
Mean	16.3 ($p=0.005$)*	42.6	2.6			14.5 ($p=0.0006$)**	37.2 ($p=0.036$)**	3.2 ($p=0.17$)**
Normal range	12.6–16.2	30.8–51.3	1.5–4.5	98–355	<10			

* Comparison between admission and control values.
** Comparison between admission and discharge values in 6 patients.
*** Patient with symptoms of bleeding.

Table 4 Haemostasis assays in one patient bitten by a death adder (S7690)

Factor (u/dl)	Level	Normal range*
Fibrinogen (d/l)	1.56	1.5–4.5
II	65	65–109
V	39	27–106
VII	59	60–182
VIII	32	33–183
IX	43	45–134
X	66	62–120
XI	53	40–107
XII	33	25–104
XIIIA	50	40–158
XIIS	51	60–140
vWF : Ag	142	53–240
Anti-thrombin III	96	69–139
Protein C	57	64–129
Plasminogen	64	98–175
Alpha-2 antiplasmin	72	80–163
Fibrinogen degradation products (μg/ml)	20	<10

* Determination in 40 PNG control subjects.

venom. In addition, antivenom appeared to have an almost immediate effect in three of the six patients in whom a response could be properly evaluated. This is consistent with Campbell's observation that paralysis was 'rapidly and completely reversed' in three patients given large amounts of antivenom (equivalent to 3–8 ampoules of death adder antivenom).[13] The apparent efficacy of the antivenom is likely to be related to the predominantly post-synaptic site of action of death adder neurotoxins. Animal experiments show that some post-synaptically-acting toxins, such as that of *Naja nigricollis*, can be displaced from the binding site, preventing blockade of the post-synaptic acetylcholine receptor,[26] and good responses to antivenom have been noted in envenoming with other predominantly post-synaptically-acting toxins.[27]

Abnormal blood coagulation results have not been reported previously in human death adder envenoming, but prolongation of the prothrombin time was noted in experimental envenoming of monkeys.[11] Previous *in vitro* testing of the venom has been inconclusive.[7–11,28] The finding of slightly altered clotting times in patients is supported by our detection of anticoagulant activity in venom of *Acanthophis sp.* from Papua New Guinea. Anticoagulant activity could be due to a phospholipase A_2 similar to that detected recently in the venom of the Papuan Black snake (*Pseudechis papuanus*).[29] The mildly raised fibrin(ogen) degradation products in one patient, (the only patient with symptoms of bleeding), and the trend towards higher fibrinogen levels on discharge, also suggest that fibrinogen breakdown may occur in some patients following bites by this species. The mechanism of this is uncertain; our *in vitro* studies showed that the venom has no direct fibrinogenolytic activity, but the possibility of a weak indirect (plasminogen-related) fibrin(ogen)olytic response can not be excluded. A reduction in platelet count has been observed previously only in patients envenomed by Australasian elapids which cause profound coagulopathy, such as brown snakes (genus *Pseudonaja*) and taipans.[30] In death adder victims, a direct venom effect upon platelet activation and agglutination, as observed *in vitro* (A. Kamiguti, unpublished observations)[31], may result in platelet depletion.

Renal failure has not been reported previously as a complication of death adder envenoming. It may have been related to myoglobinuria; the serum CK level on arrival at hospital 5 days after the bite was extremely high. However, this patient also had an extremely high venom antigen level and other postulated mechanisms of renal failure such as direct venom nephrotoxicity may have contributed. Generalized or local rhabdomyolysis was not detected clinically in our patients, but CK levels were elevated in most of them, indicating that the venom has some myotoxic activity *in vivo*. This is at odds with the reported lack of myotoxic activity of Australian death adder venom in monkeys and mice,[11,32] although some samples of *A. antarcticus* venom do contain phospholipase A activity.[10,33]

In contrast to results of our studies of envenoming by other PNG species, improvement in the management of death adder bites is more likely to be achieved by the rational use of anticholinesterases than by improving the efficacy of antivenom. The response to edrophonium in one patient, a definite improvement in hand grip and degree of ptosis, was impressive, in contrast to ten taipan patients who showed no improvement in a double-blind study of edrophonium (D.G. Lalloo, A.J. Trevett, unpublished observations). The small numbers, sporadic admissions and difficulty in the rapid identification of death adder cases precluded a formal trial of the effect of anticholinesterases. However, animal studies, published case reports and frequent clinical anecdotes suggest that anticholinesterases may be as effective in death adder envenoming as they are in Asian cobra envenoming.[34–38] The rapid improvement in the one patient in this study given both antivenom and neostigmine suggests that, in addition to effective first aid and prompt treatment, the optimal management of death adder envenoming may require both antivenom and anticholinesterases.

Acknowledgements

David Lalloo received financial support from the UNDP/World Bank/WHO Special Programme for

Research and Training in Tropical Diseases and the Rockefeller Foundation, and Andrew Trevett was supported by the Wellcome Trust. We are grateful to Dr Mark Fitzmaurice for allowing us to report on his patient.

References

1. O'Shea MT. The highly and potentially dangerous elapids of Papua New Guinea. In: Gopalakrishnakone P, Chou LM, eds. *Snakes of medical importance*. Singapore, Venom and Toxin Research Group National University of Singapore, 1990; 585–641.
2. Kellaway CH, Cherry RO, Williams FE. The peripheral action of the Australian snake venoms. *Aust J Exp Biol Med Sci* 1932; **10**:181–94.
3. Sheumack DD, Howden ME, Spence I. Isolation and partial characterisation of a lethal neurotoxin from the venom of the Australian Death adder (*Acanthophis antarcticus*). *Toxicon* 1979; **17**:609–16.
4. Kim HS, Tamaya N. Isolation, properties and amino acid sequence of a long chain neootoxin, Acanthophis antarcticus b, from the venom of an Australian snake (the common Death adder *Acanthophis antarcticus*). *Biochem J* 1981; **193**:899–906.
5. Kim HS, Tamiya N. The amino acid sequence and position of the free thiol group of a short chain neurotoxin from the common Death adder (*Acanthophis antarcticus*) venom. *Biochem J* 1981; **199**:211–18.
6. Sheumack DD, Spence I, Tyler MI, Howden ME. The complete amino acid sequence of a post-synaptic neurotoxin isolated from the venom of the Australian death adder snake (*Acanthophis antarcticus*). *Comp Biochem Physiol* 1990; **95**:45–50.
7. Kellaway CH. The actions of the venoms of the Copper-head (*Denisonia superba*) and the Death Adder (*Acanthophis antarcticus*) on the coagulation of the blood. *Med J Aust* 1929; **1**:772–81.
8. Denson KWE. Coagulant and anticoagulant action of snake venoms. *Toxicon* 1969; **7**:5–11.
9. Marshall LR, Herrmann RP. Coagulant and anticoagulant actions of Australian snake venoms. *Thromb Haemost* 1983; **50(3)**:707–11.
10. Tan NH, Ponnudurai G. A comparative study of the biological properties of Australian elapid venoms. *Comp Biochem Physiol* 1990; **97C**:99–106.
11. Sutherland SK, Campbell DG, Stubbs AE. A study of the major Australian snake venoms in the monkey (Macaca fascicularis). II. Myolytic and haematological effects of venoms. *Pathology* 1981; **13**:705–15.
12. Chester A, Crawford GPM. *In vitro* coagulant properties of venoms from Australian snakes. *Toxicon* 1982; **20(2)**:501–4.
13. Campbell CH. The Death adder (*Acanthophis antarcticus*): the effect of the bite and its treatment. *Med J Aust* 1966; **2**:922–5.
14. Sutherland SK. Genus *Acanthophis*, Death adders. In: *Australian Animal Toxins. The creatures, their toxins and care of the poisoned patient*. Melbourne, Oxford University Press, 1983.
15. Warrell DA, Davidson NMcD, Greenwood BM, Ormerod LD, Pope HM, Watkins BJ, Prentice CRM. Poisoning by Bites of the Saw-Scaled or Carpet Viper (*Echis carinatus*) in Nigeria. *Q J Med* 1977; **181**:33–62.
16. Sano-Martins IS, Fan HW, Castro SC, Tomy SC, Franca FO, Jorge MT, Kamiguti AS, Warrell DA, Theakston RD. Reliability of the simple 20 minute whole blood clotting test (WBCT20) as an indicator of low plasma fibrinogen concentration in patients envenomed by *Bothrops* snakes. *Toxicon* 1994; **32**:1045–1050.
17. Lalloo DG, Trevett AJ, Owens D, Minei J, Naraqi S, Saweri A, Hutton R, Theakston RDG, Warrell DA. Coagulopathy following bites by the Papuan Taipan (*Oxyuranus scutellatus canni*). *Blood Coagul Fibrinol* 1995; **6(1)**:65–72.
18. Theakston RDG, Lloyd-Jones MJ, Reid HA. Micro-ELISA for detecting and assaying snake venom and antibody. *Lancet* 1977; **ii**:639–41.
19. Ho M, Warrell MJ, Warrell DA, Bidwell D, Voller A. A critical reappraisal of the use of enzyme-linked immunosorbent assays in the study of snake bite. *Toxicon* 1986; **24**:211–21.
20. Lalloo D, Trevett A, Black J, Mapao J, Naraqi S, Owens D, Hutton R, Theakston RDG, Warrell DA. Neurotoxicity and haemostatic disturbances in patients envenomed by the Papuan Black snake (*Pseudechis papuanus*). *Toxicon* 1994; **32(8)**:927–36.
21. Laemmli UK. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature* 1970; **227**:680–5.
22. Slater KR. *A guide to the dangerous snakes of Papua*. Port Moresby, Government Printer, 1968.
23. Tidswell F. *Researches on Australian Venoms, Snake-bite, Snake-venom and Antivenene: The poison of the Platypus, The poison of the Red-spotted spider*. Sydney, NSW Department of Public Health, 1906.
24. Lalloo DG, Trevett AJ, Korinhona A, Nwokolo N, Laurenson I, Paul M, Black J, Naraqi S, Mavo B, Saweri A, Hutton RA, Theakston RDG, Warrell DA. Snakebites by the Papuan taipan (*Oxyuranus scutellatus canni*); paralysis, haemostatic and electrocardiographic abnormalities and effects of venom. *Am J Trop Med Hyg* 1995; in press.
25. Campbell CH. The effects of snake venoms and their neurotoxins on the nervous system of man and animals. In: Hornabrook RW, ed. *Topics in Tropical Neurology*. Philadelphia, Davis, 1975:259–93.
26. Gatineau E, Lee CY, Fromageot P, Menez A. Reversal of snake neurotoxin to mammalian acetylcholine receptor by specific antiserum. *Eur J Biochem* 1988; **171**:535–9.
27. Watt G, Meade BM, Theakston RDG, Padre L, Tuazon ML, Calubaquib C, Santiago E, Ranoa CP. Comparison of Tensilon and antivenom for the treatment of cobra-bite paralysis. *Trans Roy Soc Trop Med Hyg* 1989; **83**:570–573.
28. Kaire GH. A heat-stable anticoagulant in snake venoms. *Med J Aust* 1964; **2**:972.
29. Kamiguti AS, Laing GD, Lowe GM, Zuzel M, Warrell DA, Theakston RDG. Biological properties of the venom of a rare elapid, the Papuan black snake *(Pseudechis papuanus)*; presence of a phospholipase A2 inhibitor. *Toxicon* 1994; **32**:915–25.
30. White J. Thrombocytopenia after snake envenomation. *Med J Aust* 1990; **152**:445–446.
31. Marshall LR, Herrmann RP. Australian snake venoms and their in vitro effect on human platelets. *Thromb Res* 1989; **54**:269–75.
32. Mebs D, Samejima Y. Purification, from Australian elapid

venoms, and properties of phospholipases A which cause myoglobinuria in mice. *Toxicon* 1980; **18**:443–54.

33. Doery HM, Pearson J. Haemolysins in Venoms of Australian Snakes. *Biochem J* 1961; **78**:820–7.
34. Flaschenberger W, Mirtschin PJ. Anticholinesterases as antidotes to envenomation of rats by the death adder (*Acanthophis antarcticus*). *Toxicon* 1994; **32(1)**:35–9.
35. Hudson BJ. Positive response to edrophonium in death adder (*Acanthophis antarcticus*) envenomation. *Aust NZ J Med* 1988; **18**:792–4.
36. Currie B, Fitzmaurice M, Oakley J. Resolution of neurotoxicity with anticholinesterase therapy in death-adder envenomation. *Med J Aust* 1988; **148**:522–5.
37. Watt G, Theakston RDG, Hayes CG, Yambao ML, Sangalang R, Ranoa CP, Alquizalas E, Warrell DA. Positive response to edrophonium in patients with neurotoxic envenoming by cobras (*Naja naja philippinensis*). *N Engl J Med* 1986; **315**:1444–8.
38. Currie BJ, Richens J, Korinhona A, Worthington J. Anticholinesterase therapy for death adder envenomation. *Aust NZ J Med* 1990; **20**:190.