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SNAKE BITES BY THE PAPUAN TAIPAN (*OXYURANUS SCUTELLATUS CANNI*): PARALYSIS, HEMOSTATIC AND ELECTROCARDIOGRAPHIC ABNORMALITIES, AND EFFECTS OF ANTIVENOM

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Abstract. One hundred sixty-six patients with enzyme immunoassay–proven bites by taipans (*Oxyuranus scutellatus canni*) were studied in Port Moresby, Papua New Guinea. One hundred thirty-nine (84%) showed clinical evidence of envenoming: local signs were trivial, but most developed hemostatic disorders and neurotoxicity. The blood of 77% of the patients was incoagulable and 35% bled spontaneously, usually from the gums. Fifty-one per cent had microscopic hematuria. Neurotoxic signs (ptosis, ophthalmoplegia, bulbar paralysis, and peripheral muscular weakness) developed in 85%. Endotracheal intubation was required in 42% and mechanical ventilation in 37%. Electrocardiographic abnormalities (sinus bradycardia and septal T wave inversion) were found in 52% of a group of 69 unselected patients. Specific antivenom raised against Australian taipan venom was effective in stopping spontaneous systemic bleeding and restoring blood coagulability but, in most cases, it neither reversed nor prevented the evolution of paralysis even when given within a few hours of the bite. However, early antivenom treatment was associated statistically with decreased incidence and severity of neurotoxic signs. The low case fatality rate of 4.3% is attributable mainly to the use of mechanical ventilation, a technique rarely available in Papua New Guinea. Earlier use of increased doses of antivenoms of improved specificity might prove more effective.

Taipans (genus *Oxyuranus*) are the world's deadliest snakes. The mouse subcutaneous 50% median lethal doses (LD_{50s}) are 0.010 mg/kg for venom of the Australian inland taipan (*O. microlepidotus*), 0.0505 mg/kg for the Papuan taipan (*O. scutellatus canni*) (Figure 1), and 0.064 mg/kg for the Australian taipan (*O. s. scutellatus*),[1] lethal potencies 10–50 times greater than black mamba venom and 20–140 times greater than king cobra venom.[2] Before the introduction of antivenom in 1955, taipan bites in Australia were considered almost invariably fatal.[1] Compared with its Australian cousin, the Papuan taipan grows longer (to more than 3 meters) and yields more venom when milked (up to 400 mg dry weight).[3] It inhabits the southern coast of Irian Jaya and Papua New Guinea. In the Central Province and the National Capital District of Papua New Guinea, it is responsible for more than 80% of all snake bites, with an annual mortality rate of 3.7 per 100,000 population (Currie B, unpublished data).[4,5] Taipan venom contains taipoxin, a phospholipase A_2 presynaptic toxin and myotoxin; other presynaptic and postsynaptic toxins; taicatoxin, a calcium channel blocker; and a prothrombin activator.[6–9] Case reports of bites by *O. s. scutellatus* and of six bites by *O. s. canni* have been published.[1,3] In the present study, we describe clinical and laboratory features of 166 cases of proven *O. s. canni* bites and the effects of treatment.

PATIENTS AND METHODS

All patients presenting with a history of snakebite to Port Moresby General Hospital between March 1990 and June 1992 were studied prospectively. Medical history and results of a physical examination were recorded on standard forms. Blood was taken for hematologic and biochemical investigations, and 2 ml of whole blood was placed in a new, clean, dry, glass tube for use in the 20-min whole blood clotting test (20 WBCT).[10] 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 a dipstick procedure.

Patients with signs of envenoming (incoagulable blood [20 WBCT], neurotoxicity, spontaneous systemic bleeding, or lymph node tenderness) were treated with one ampule of either polyspecific or monospecific taipan antivenom (Commonwealth Serum Laboratories, Melbourne, Australia) diluted to a total volume of 100 ml and infused intravenously over a 20-min period. Promethazine (12.5 or 25 mg intravenously) was given before antivenom to prevent reactions. Patients were examined at least every 6 hr for the first 36 hr and the 20 WBCT was repeated every 6 hr until blood became coagulable.

Venom detection. Samples were tested with antisera against the venoms of the five important species of venomous snakes found in Papua New Guinea: taipan (*O. s. canni*), Papuan black snake (*Pseudechis papuanus*), death adder (*Acanthophis* sp.), common brown snake (*Pseudonaja textilis*), and small-eyed snake (*Micropechis ikaheka*) in an enzyme immunoassay (EIA).[11,12] Background absorbance was established by assaying 105 control samples from Papua New Guineans never bitten by snakes. For the taipan, the EIA specificity was 87%, and the lower limit of detection was 2.5 ng/ml. A taipan bite was diagnosed when a significant concentration of *O. s. canni* venom antigen alone was detected.

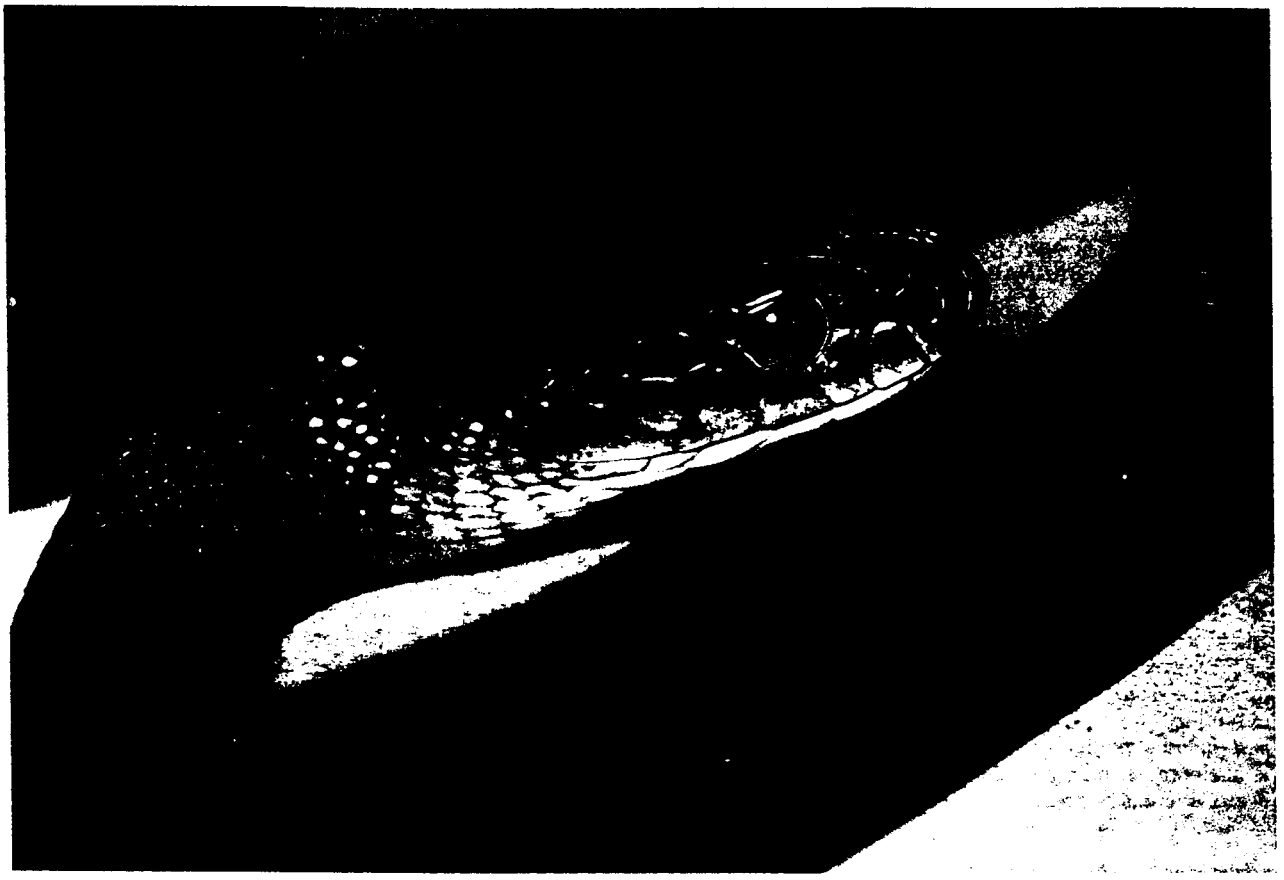

FIGURE 1. Papuan taipan (*Oxyuranus scutellatus canni*); a 1.5-meter long specimen from Central Province, Papua New Guinea.

Statistical methods. The time between being bitten and treatment with antivenom was compared between groups of patients by calculation of confidence intervals for the ratio of the means of the log transformed data using the *t* distribution and the SPPS for Windows statistical package (SPSS Inc., Chicago, IL). The Mann-Whitney U test was used to compare creatine kinase levels in different groups.

RESULTS

One hundred sixty-six (49.6%) of 335 patients presenting with snakebite over 27 months were shown by EIA to have been bitten by taipans. Of this subgroup, 139 (83.7%) had symptoms and signs of envenoming. Taipans were responsible for 83.2% of all cases of envenoming in which the biting species was identified; *Acanthophis* sp. 10.8%, *P. papuanus* 4.2%, *Pseudonaja textilis* 1.8%, and *M. ikaheka* 0%. Only two envenomed patients killed and brought the taipans responsible (the snakes were approximately 1.5-m long).

Sixty-three percent of the patients were males. Their mean age was 25.2 years (range 2–62); 22 patients (13.3%) were younger than 12 years of age. All but six (3.6%) were bitten on a lower limb, usually while gardening or walking on bush paths. Although 85% were bitten in daylight, only 13 (7.8%) could give a convincing description of the taipan. First aid was reported by 80 (66.1%) patients, and was most commonly either loosely tied tourniquets or razor cuts around the bite. Pressure bandages were applied in only five patients. There was no suggestion that the first aid measures used had any effect on outcome. Patients reached hospital between 0.5 and 50 hr (median 3.5) after the bite.

Symptoms began 15 min–6 hr (median 1 hr) after the bite (Table 1). Spontaneous systemic bleeding often began within an hour of the bite, but neurologic symptoms were usually delayed for at least 2 hr (median 6). Twenty-three per cent collapsed soon after the bite: unconsciousness was usually transient but could last for several minutes. One patient complained of muscle pain and tenderness.

Two small fang marks were sometimes visible. Tender enlargement of regional lymph nodes was common (Table 2). Spontaneous systemic bleeding was usually from gingival sulci. Only two patients had retinal hemorrhages. Patients with incoagulable blood bled from superficial first aid cuts, from venipuncture sites, and most spectacularly, from fresh grazes, incurred when they collapsed after the bite. Microcopic hematuria was detected in 28 (50.9%) of 55 cases examined. Blood was incoagulable (20 WBCT) as early as 30 min after the bite and by the time of admission in 77%.

Neurologic signs progressed from ptosis to external ophthalmoplegia and bulbar involvement, with dysarthria and difficulty in mouth opening (Figure 2). Bulbar paralysis necessitated intubation in 41.7% of the patients and progressed to respiratory paralysis requiring mechanical ventilation in 36.7% (Table 2 and Figure 3). Peripheral muscle weakness developed and some patients became totally paralyzed. In 83% of the patients, neurotoxicity was maximal

TABLE 1

*Symptoms on admission in patients envenomed by taipans (n = 120–135)**

	No. (%)
General	
Lymph node pain	106 (84.1)
Headache	67 (54.5)
Abdominal pain	76 (59.8)
Vomiting	85 (64.4)
Collapse	23 (19.2)
Drowsiness	38 (31.7)
Bleeding	
Systemic	59 (43.7)
Mouth	50 (37.0)
Nose	2 (1.5)
Vomit	17 (12.6)
Local (bite site)	22 (16.3)
Neurologic	
Ptosis	84 (64.1)
Diplopia	26 (21.7)
Dysphagia	39 (31.5)
Dysarthria	39 (32.2)
Dyspnoea	17 (14.0)

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

within 24 hr of the bite; the median time to intubation was 13.5 hr (range 3–55). Paralyzed patients remained fully conscious unless given sedative drugs.

Thirty-two (24.1%) of the patients had bradycardia (< 55 beats/min) during admission, but hypotension was rare. Electrocardiograms (ECGs) were abnormal in 36 of 69 unselected patients; the commonest abnormalities were bradycardias and septal T wave inversion (Table 3 and Figure 4). Eight patients (5.8%) developed acute renal dysfunction (creatinine level > 270 μmol/L). None was obviously dehydrated, hypotensive, or had muscle tenderness or dark urine. Renal function recovered with conservative treatment except in one case requiring peritoneal dialysis.

Laboratory results. *Hematology and biochemistry.* Hematologic and biochemical test results are shown in Table 4. The neutrophil count was usually elevated on admission. Lymphopenia (< 1 / 10^9/L) occurred in eight (17.8%) of 45 patients. Platelet counts reached their nadir 1–2 days after the bite. Patients with coagulopathy had prolongation of prothrombin and partial thromboplastin times and depletion of fibrinogen. Maximum serum creatine kinase levels normally occurred on the first or second day after admission; higher peak levels were significantly associated with the need for intubation (median 564 versus 325 IU/L; $P = 0.023$). Plasma myoglobin, measured in 26 patients, and serum creatine kinase levels were positively correlated.

Urine findings. Proteinuria (83.3%), microscopic hematuria (50.9%), and hemoglobinuria/myoglobinuria detected using BM-test 7 strips (Boehringer Mannheim, Indianapolis, IN) (38.5% of those with no red blood cells seen by microscopy) were all common. More than half of the patients examined had granular casts and 56.4% had white blood cells in the urine.

Response to treatment. One hundred twenty-eight patients (92.1%) were treated with antivenom 0.75–66 hr (median 5) after the bite. Two of the other 11 patients were paralyzed, but there was no antivenom available; the remainder presented with mild signs more than 24 hr after the bite and therefore were not given antivenom. Initially, eight of the 128 patients were given black snake or death adder antivenom inappropriately because they had misidentified the snake. Twenty patients received a second ampule of antivenom to assess the effects of increased dosage on the coagulopathy in five patients, rapid deterioration in the level of neurotoxicity in four, severe bleeding or persisting incoagulable blood in three, and for uncertain indications at the health center in three.

Spontaneous systemic bleeding had often stopped before treatment and rarely persisted for more than 3 hr after treatment with antivenom. Blood became coagulable (20 WBCT) by 12 and 18 hr after treatment with antivenom in 80% and 93% of the patients, respectively. However, there was little

TABLE 2

*Signs in patients envenomed by taipans (n = 105–139)**

	On admission No. (%)		On admission No. (%)	Eventual No. (%)
General		Neurologic		
Swelling of bite site	3 (2.2)	Ptosis	70 (53.8)	117 (85.4)
Tender lymph nodes	123 (91.1)	Ophthalmoplegia	48 (39.0)	105 (76.6)
Abdominal tenderness	65 (48.1)	Jaw restriction†	17 (20.5)	40 (54.1)
		Slurred speech†	37 (35.2)	67 (60.9)
Bleeding				
Systemic	48 (35.0)	Diminished reflexes†	14 (21.2)	43 (33.6)
Mouth	42 (30.7)	Diminished hand grip†	12 (18.8)	73 (57.9)
Nose	3 (2.2)	Intubation	– –	58 (41.7)
Vomit	17 (12.4)	Ventilation	– –	51 (36.7)
Local				
From bite site	10 (7.3)			
Cuts	9 (6.6)			
Grazes	6 (4.4)			
Venipuncture	12 (8.8)			
Incoagulable blood (20 WBCT)‡	104 (77.0)			

* – = sign is not appropriate at this time; the patient could not be ventilated upon admission.
† Examined in a smaller number of patients.
‡ 20 WBCT = 20-min whole blood clotting test.

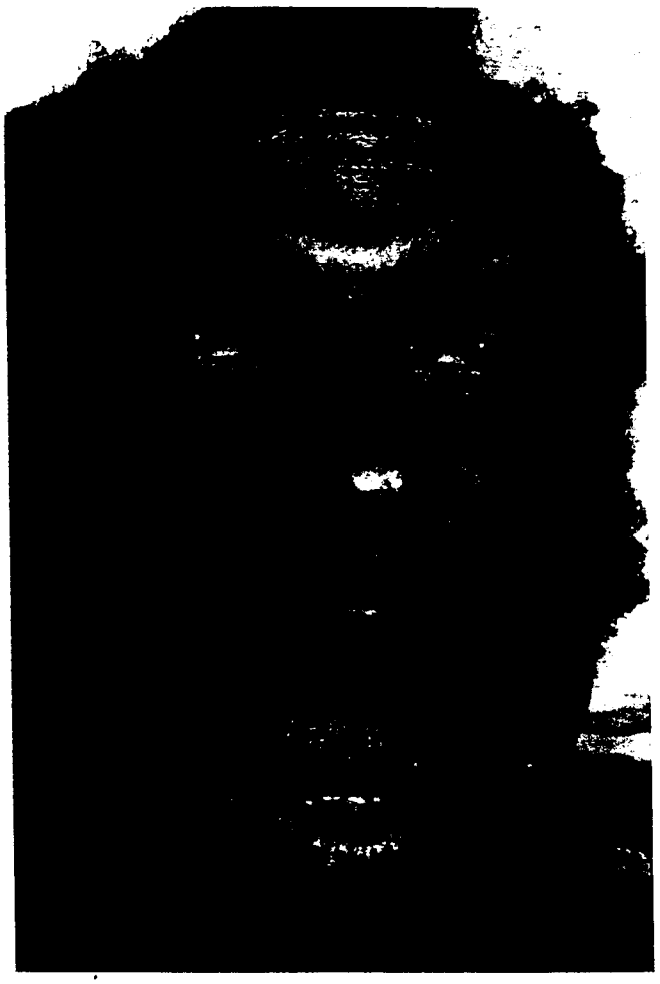

FIGURE 2. Melanesian man showing early signs of neurotoxicity (ptosis and ophthalmoplagia) and spontaneous bleeding from the gums 5.5 hr after being bitten by a Papuan taipan.

FIGURE 3. The same patient in Figure 2 24 hr later. Specific antivenom has corrected the hemostatic abnormalities but neurotoxicity has progressed to almost total flaccid paralysis (note complete ptosis) requiring mechanical ventilation.

clinical evidence that neurotoxicity responded to antivenom. After antivenom treatment, no patient improved within 6 hr, 25 (18.9%) developed their first signs of neurotoxicity, and 48 (37.2%) deteriorated. Both the risk of developing neurotoxicity and its severity (measured by the need for intubation) correlated with the time interval between the bite and treatment (geometric mean time 2.72 versus 6.24 hr, ratio of means = 2.29, 95% confidence limits = 1.49–3.26, $P < 0.0001$ and geometric mean 4.13 versus 8.22 hr, ratio of means = 1.99, 95% confidence limits = 1.49–2.65, $P < 0.0001$), respectively. Thirteen of the 16 patients who did not develop neurotoxicity had been treated within 4 hr of the bite. Intubation was necessary in only 13.3% of the patients treated within 4 hr of the bite compared with 63% of those treated later.

Speed of recovery depended upon the severity of the neurotoxicity. In severely envenomed patients, the first sign of recovery was usually a flicker of lateral eye movement 9–92 hr (median 48) after the bite. Patients required intubation for 3–176 hr (median 88).

Only six patients died, giving a case fatality rate of 4.3%; two of them were moribund on admission. Two of the other four died unexpectedly, probably of sudden neurologic deterioration and respiratory arrest. One patient developed anoxic brain damage after a difficult intubation and an elderly patient with concomitant tuberculosis died suddenly in the hospital several days after recovering from severe neurotoxicity. There were few serious sequelae, although one patient had a probable cerebral hemorrhage with eventual recovery and another was admitted unconscious with a history and signs suggestive of cerebral anoxia; this patient remains severely handicapped. A number of patients developed respiratory infections, often related to delayed intubation and presumed aspiration. Sensory loss within a radius of 2–3 cm of the bite site was common and sometimes persisted for several weeks.

Two severely envenomed patients who could not be given antivenom developed more severe sequelae. One required intubation for 120 hr and still had severe proximal muscle weakness at the time of discharge. The other, a young girl, never recovered adequate ventilatory muscle function and eventually died while still being ventilated three weeks after the bite.

TABLE 3

*Electrocardiographic findings in 69 of the 139 patients envenomed by taipans**

	No. (%)
Normal	29 (42.0)
Unrelated abnormality	4 (5.8)
Septal T wave changes	22 (31.9)
ST segment changes	3 (4.3)
Sinus bradycardia (<55)	9 (13.0)
Bradycardia/first degree AV block	2 (2.9)
Bradycardia/bundle branch block	1 (1.4)
Intraventricular conduction defect	2 (2.9)
Complete heart block	1 (1.4)
Atrial arrhythmias	2 (2.9)
Frequent ventricular ectopics	1 (1.4)

* Four patients had T wave changes and a sinus bradycardia, two patients had T wave changes and first degree atrioventricular (AV) block, and one patient had T wave changes and an intraventricular conduction defect.

DISCUSSION

Taipans proved to be the most important cause of snake bite morbidity and mortality in this region of Papua New Guinea. Principal signs of envenoming were bleeding, incoagulable blood, paralysis, and ECG abnormalities. More than three-fourths of the patients had incoagulable blood detectable at bedside by the 20 WBCT, a simple and practical indicator even of recent envenoming. Most of the other patients had coagulation abnormalities detectable by more sensitive tests. Spontaneous systemic bleeding was common, in contrast to most of the Australian case reports[1] (White J, unpublished data), and can be attributed to hemorrhagin, profound coagulopathy, thrombocytopenia, and perhaps, platelet dysfunction. Taipan venom causes platelet aggregation and activation in vitro.[13] Thrombocytopenia also probably results from coagulopathy and intense defibrinogenation. Spontaneous bleeding was rarely of clinical significance and often stopped spontaneously before admission. In most patients, the coagulopathy resolved rapidly after treatment with antivenom. Even in untreated patients, the coagulopathy resolved within two days, whereas patients bitten by Malayan pit vipers (*Calloselasma rhodostoma*) or saw-scaled vipers (*Echis ocellatus*) have persisting coagulopathy for up to two weeks.[10, 14]

The failure of antivenom to improve or even prevent neurotoxicity in most patients contrasts with experience of patients bitten by death adders, in whom there was often rapid marked improvement within several hours of treatment.[15] The high proportion of patients needing ventilatory support despite treatment with antivenom is of great concern in a country where facilities for mechanical ventilation are restricted to a few of the larger hospitals. In monkey experiments, circulating taipan venom is detectable within 15 min of subcutaneous administration, although most venom components are absorbed via the lymphatic system.[16] Taipoxin, the major neurotoxin, acts presynaptically to reduce the release of acetylcholine from the presynaptic membrane after a latent period. Ultrastructural studies suggest that the toxin damages the motor end plate and muscle (explaining the modest increase in muscle enzyme and myoglobin levels in our patients).[17–19] In vitro experiments also suggest that the binding of taipoxin to cell surface sites is poorly reversible and that following nerve stimulation, bound toxin is no longer accessible to neutralizing antibodies.[20]

The longer the delay between bite and antivenom treatment, the greater the risk and severity of neurotoxicity. This suggests that antivenom does have an effect if given soon enough, but once toxin has bound to the end plate, antivenom may no longer be effective; a poor response to antivenom is a feature of poisoning by a number of venoms containing presynaptically active toxins.[21, 22] Even some patients treated within an hour of the bite developed neurotoxicity. Most received one ampule containing 12,000 units of taipan antivenom. This may be inadequate to neutralize high doses of injected venom. The antivenom currently used in Papua New Guinea is raised against venom from Australian taipans, which is less toxic than Papuan taipan venom and may have a different protein composition.[1] Australian antivenom might therefore be less effective in neutralizing *O. scutellatus canni* venom than *O. s. scutellatus* venom.

Envenoming by several species of Australasian elapids

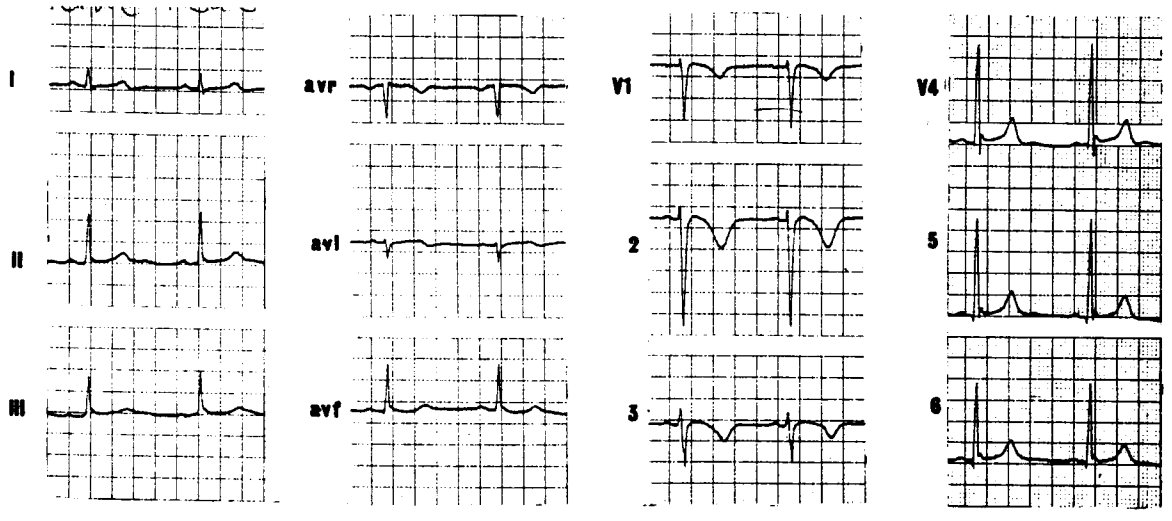

FIGURE 4. Septal T wave inversion in a snakebite patient on admission 22 hr after the bite.

TABLE 4

Hematologic and biochemical measurements in patients envenomed by taipans

Finding	No. abnormal/no. tested (%)	Mean	Range
White cell count			
Admission, >12,000 × 10^6/L	55/107 (51.4)	13,240	1,600–33.500
Peak, >12,000 × 10^6/L	66/125 (52.8)	13,240	4,700–33,500
Platelet count			
Admission, <100 × 10^9/L	13/103 (12.6)	166.7	60–466
Nadir, <100 × 10^9/L	30/109 (27.5)	136.5	147–363
Creatine kinase			
Admission, >250 IU/L	33/68 (48.5)	389.0	11–2,175
Peak, >250 IU/L	68/91 (74.7)	765.0	43–8,110
Myoglobin			
Admission, >80 ng/ml	12/23 (52.2)	153.8	15–976
Aspartate transaminase			
Admission, >50 IU/L	42/104 (40.4)	53.6	18–322
Peak, >50 IU/L	61/116 (52.6)	70.4	18–433

has caused renal failure attributed to rhabdomyolysis, direct venom nephrotoxicity, and disseminated intravascular coagulation.[23–26] Although taipoxin is strongly myolytic in vitro, clinical evidence of myotoxicity (muscle pain and tenderness) was rare in our patients, gross myoglobinuria was not observed and serum creatine kinase and plasma myoglobin concentrations were not markedly elevated in most patients. Disseminated intravascular coagulation or venom nephrotoxicity may have contributed to renal dysfunction.

Electrocardiographic abnormalities have not been reported previously in victims of taipan bites, although *Pseudonaja textilis* envenoming has caused QRS widening in humans and EGG changes in dogs.[27,28] Taipan venom contains taicatoxin,[8] a slow calcium channel blocker, which might affect cardiac muscle, but the apparent localization of repolarization changes in the septal region is difficult to explain by such a mechanism. In dogs, the prothrombin activator of *Pseudonaja textilis* venom caused coronary thrombosis; thus intravascular coagulation and microthrombi may be responsible for the EGG changes.[29]

The low mortality in our patients was attributable largely to the use of mechanical ventilation; many patients die following snakebite in more remote areas. Increasing the availability of antivenom in peripheral areas would allow earlier treatment, possibly limiting severe neurotoxicity, but the cost of antivenom precludes the use of increased doses. The best chance of improving the outcome after taipan bites in Papua New Guinea lies in the use of specific first aid measures, such as the compression immobilization method advocated in Australia,[30] the early use of antivenoms of improved specificity, and the discovery of effective ancillary pharmacologic treatments.

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