Electrophysiological findings in patients envenomed following the bite of a Papuan taipan (*Oxyuranus scutellatus canni*)

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Abstract

Electrophysiological studies were done on patients with systemic neurotoxicity following the bite of a Papuan taipan (*Oxyuranus scutellatus canni*). Evoked compound muscle action potentials decreased and increased in tandem with clinical deterioration and recovery. Nerve conduction velocities did not change in envenomed patients and were consistent with control studies. Repetitive nerve stimulation studies showed decremental responses in envenomed patients with post-tetanic potentiation followed by post-tetanic exhaustion. The findings are consistent with studies *in vitro* which suggested that the major action of neurotoxins in Australian taipan venom is at the synapse. The observation that electrophysiological data correlate closely with the clinical condition of the patient has potential application in the assessment of interventions in the management of snake bite victims.

Keywords: snake bite, *Oxyuranus scutellatus canni*, electrophysiological observations

Introduction

The venom of the Papuan taipan (*Oxyuranus scutellatus canni*) contains neurotoxins, a prothrombin activator and a specific complex calcium channel blocker. Clinical effects of envenoming include a profound consumption coagulopathy and progressive systemic neuromuscular paralysis (LALLOO *et al.*, 1993). Between May 1991 and May 1993, 143 patients were admitted to Port Moresby General Hospital (PMGH), Papua New Guinea with systemic envenoming following the bite of a Papuan taipan. Sixty-eight of these patients (48%) developed severe neurotoxicity requiring ventilation, despite the majority of them (55) being treated with appropriate antivenom. The median duration of ventilation required was 68 h (range 6–500 h).

The clinically most significant neurotoxin in taipan venom is believed to be taipoxin, a trimeric phospholipase A_2 neurotoxin which inhibits the release of acetylcholine from presynaptic cholinergic nerve terminals (KAMENSKAYA & THESLEFF, 1974) and produces structural changes in the nerve terminal (CULL-CANDY *et al.*, 1976). The presence of other phospholipase neurotoxins and a post-synaptic neurotoxin has also been demonstrated (FOHLMAN *et al.*, 1976; MEBS *et al.*, 1979; LAMBEAU *et al.*, 1989). As a preface to studies on the effect of pharmacological interventions in treating neurotoxicity caused by taipan bite, a series of electrophysiological studies was undertaken with patients envenomed by the Papuan taipan.

Patients and Methods

Patients included in this study gave a history of snake bite, had unequivocal signs of envenoming, and gave informed consent to participate in the study. Pregnant women and children under the age of 14 years were excluded. All the patients had taipan venom antigen detected by enzyme immunoassay in at least one of the following specimens: admission serum sample, bite site swab, or bite site aspirate using the method described by THEAKSTON *et al.* (1977) as modified by HO *et al.* (1986). The following studies were carried out.

Motor nerve conduction studies in median and ulnar nerves

(i) Measurement of compound muscle action potential (CMAP) amplitude.

(ii) Measurement of F wave latencies.

(iii) Calculation of motor conduction velocities.

Sensory nerve conduction studies in median and ulnar nerves

(i) Measurement of sensory nerve action potentials (SNAP).

(ii) Calculation of sensory nerve conduction velocities.

Repetitive nerve stimulation studies (RNS).

(i) Recording the change in CMAP amplitude recorded in abductor digiti minimi after a train of stimuli at 3 Hz to the ulnar nerve at the wrist.

Sequential grip strength readings using a hand-held dynamometer.

Median and ulnar nerve motor studies were performed using surface electrodes and recording over abductor pollicis and abductor digiti minimi respectively after a supramaximal stimulus. Conduction velocities were determined by standard means using 2 points of stimulation. The positions of stimulating and recording electrodes were marked and identical positions used in subsequent studies. F wave values were recorded by supramaximally stimulating the ulnar nerve and measuring the shortest latency of 10 responses recorded over abductor digiti minimi. Sensory amplitudes and conduction velocities were measured by stimulating the digital branches of median and ulnar nerves in the palm at a distance of 8 cm from recording electrodes placed over the mixed nerves at the wrist. RNS were performed by stimulating the ulnar nerve at the wrist at a frequency of 3 Hz and recording the change in amplitude of the evoked CMAP over abductor digit minimi after a train of 9 stimuli. In a small number of patients and controls, the RNS study was repeated after stimulating the nerve at 50 Hz for 5 seconds. A stimulus duration of 0·1 msec was used for all studies. Filter settings were 2 Hz–10 kHz and 20 Hz–2 kHz for motor and sensory studies respectively. CMAP amplitudes were calculated from baseline to the peak of the negative deflection.

The clinical severity and rate of progression of envenoming varied considerably between patients. The values for envenomed patients compared with control studies were recorded at peak neurotoxicity in patients who had envenoming of sufficient severity for them to have required intubation with or without ventilation. The time after envenoming at which patients reached this stage varied considerably.

Control data were collected from 26 fit Melanesian volunteers. The same sequence of studies was performed in both right and left arms of all subjects except one who had a previous wrist injury. Patients and controls were age and height matched for comparison of F wave values.

All studies were performed using a Medelec Neurostar® MS92B EMG machine at the bedside in the intensive care or high dependency wards at PMGH. Control studies were done in the research laboratory in the department of clinical sciences at the hospital. Room temperatures varied between 24°C and 26°C. No attempt was

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made to control for skin temperature, although patients who had clinical evidence of peripheral vasoconstriction were not included. Grip strength measurements were made using a hand held dynamometer (Lafayette, Indiana, USA) and expressed as the mean of 3 readings. The study had the approval of the national ethics committee of Papua New Guinea.

Statistics

Numerical data were stored using the Epi-Info statistics package (USD, Georgia, USA) and the Lotus R123® spreadsheet. Statistical analysis was performed using the Instat® biostatistics package (GraphPad® Software). The results of sensory and motor conduction studies are presented as mean values with twice their standard errors. Where appropriate, continuous variables were compared using the unpaired *t* test. 95% confidence limits for calculated means and significance levels are given.

Results and Discussion

The results are shown in Tables 1–3 and Figs. 1–3. Sequential readings of CMAP amplitudes recorded from abductor pollicis after stimulation of the median nerve showed a similar pattern of decline and recovery (Fig. 1).

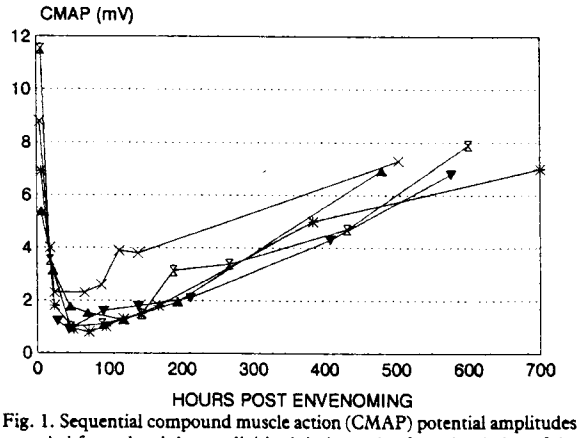

Fig. 1. Sequential compound muscle action (CMAP) potential amplitudes recorded from the abductor digiti minimi muscle after stimulation of the ulnar nerve in 5 patients after being bitten by a Papuan taipan; all 5 required ventilation.

The motor and sensory nerve conduction velocities and evoked CMAP amplitudes in Melanesian controls (Table 1) were similar to those reported from Caucasian subjects (KIMURA, 1989). In envenomed patients there was a significant reduction in CMAP amplitude ($P<0.0001$) (Table 2) but no significant change in motor conduction velocity (Table 1). Sensory nerve conduction velocities were not significantly affected by envenoming but sensory nerve action potentials were marginally reduced in severely envenomed patients ($P<0.01$). The motor findings were consistent with observations *in vitro* that the main effect of the neurotoxins in taipan venom is on synaptic transmission (KAMENSKAYA & THESLEFF, 1974) and do not show any evidence of an effect on axonal transmission (Table 1). The sensory abnormalities were more of a surprise (Table 1). Loss of sensation around the bite site is a common finding in Papuan taipan bite but other sensory abnormalities have not been described. Loss of taste and smell has been reported in a small number of patients envenomed by the Australian taipan (*O. s. scutellatus*) (FLECKER, 1944; REID & FLECKER, 1950; WHITE, 1987) but we have not found this, or any clinical evidence of sensory neuropathy distant from the bite site, in Papuan patients. Extrinsic factors such as decreased peripheral perfusion in ventilated patients may have influenced the sensory studies. More detailed studies of sensory conduction are needed to assess the significance of these observations.

Table 1. Sensory and motor nerve conduction studies in controls and envenomed patients with severe neurotoxicity

	Median nerve		Ulnar nerve	
	Controls[a]	Envenomed[a]	Controls[a]	Envenomed[a]
No.	51	24[b]	51	24[b]
Motor conduction velocity (m/s)	60·0 (1·0)	59·0 (2·2)	63·8 (1·3)	58·8 (2·4)
CMAP[c] amplitude (mV)	9·8 (0·7)	2·1 (0·6)	8·7 (0·8)	2·5 (0·7)
F wave (matched) (m/s)	–	–	26·1 (0·8)	26·1 (0·9)
Sensory conduction velocity (m/s)	58·2 (1·6)	55·4 (3·1)	56·0 (2·3)	55·4 (3·8)
SNAP[d] amplitude (μV)	43·0 (1·6)	30·7 (4·7)	23·4 (4·5)	13·1 (3·4)

[a]Mean values (2× standard error of the mean in parentheses).
[b]Sensory studies and F wave values obtained for 16 patients only.
[c]Compound muscle action potential.
[d]Sensory nerve action potential.

Table 2. Changes in compound muscle action potential amplitude during a train of 9 stimuli at 3 Hz in control patients and in envenomed patients with significant neurotoxicity

	No.	Mean change (%)[a]
Controls	22	104·2 (102·5–105·9)
Envenomed patients (stage 4/5)	16	92·5 (88·5–96·5)

[a]95% confidence intervals in parentheses.

The majority of envenomed patients had a decremental response on RNS testing at a frequency of 3 Hz. Decremental responses were not seen in control patients (Table 3; $P<0.001$).

Table 3. The effect of 5 sec stimulation at 50 Hz on a subsequent train of 9 stimuli at 3 Hz and the relationship between the amplitude of the first post-tetanic and the initial pre-tetanic compound muscle action potential

	No.	Ratio of 9th to 1st post-tetanic value (%)[a]	Ratio of 1st post-tetanic to 1st pre-tetanic value (%)
Controls	15	106·5 (104·6–108·4)	103
Envenomed patients (stage 4/5)	9	66·7 (51·9–81·4)	174

[a]95% confidence intervals in parentheses.

After tetanic stimulation, there was more post-tetanic potentiation in envenomed patients than in controls and a significant increase in the degree of decrement. These findings are consistent with significantly impaired neuromuscular transmission but do not distinguish between a pre- and post-synaptic block. The speed of onset of neuromuscular blockade by taipoxin *in vitro* is significantly enhanced by stimulation of the nerve and the depletion of synaptic vesicles has also been shown to be related to nerve activity (CULL-CANDY *et al.*, 1976; CHANG *et al.*, 1977). Similarly, repetitive stimulation of the nerve may deplete synaptic vesicles resulting in a decremental response. It is impossible to say whether the post-tetanic potentiation results from increased transmitter release from predominantly unaffected nerve terminals or an ef-

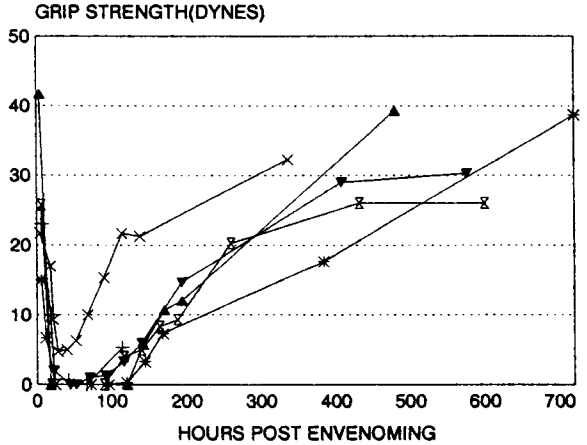

Fig. 2. Sequential grip strength readings of the 5 envenomed patients shown in Fig. 1.

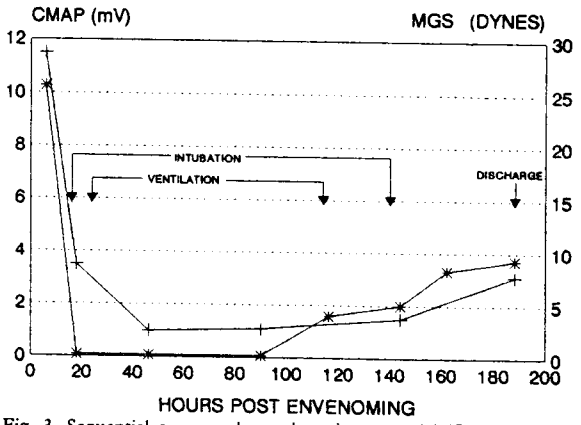

Fig. 3. Sequential compound muscle action potential (CMAP; +) and mean grip strength readings (MGS; *) values in a patient bitten by a Papuan taipan and given antivenom 6 h after envenomation.

fect in overcoming the inhibitory effect of the toxins. The precise mechanism by which taipoxin inhibits transmitter release is not known but it appears that it may interrupt vesicle membrane recycling.

The decline and recovery of evoked CMAP amplitudes correlated closely with hand grip strength measurements taken at the same time (Figs 2, 3). As neurotoxicity progressed and patients required intubation and ventilation, both measurements approached their nadir. Recovery of CMAP amplitudes and grip strength measurements to their maximum values took between 2 and 3 weeks in the most severely envenomed patients. The time course of recovery is consistent with resprouting of nerve terminals damaged by toxin. Concentric needle electromyography was done on several patients at follow-up; the motor unit architecture appeared relatively normal, which also suggests that toxin-induced damage is localized to the nerve terminals. The close correlation between clinical events and electrophysiological findings provides a simple and objective means of assessing interventions in the management of neurotixicity following snake bite.

Acknowledgements

We thank Ms Alison Richards of the Liverpool School of Tropical Medicine for doing the immunoassays. We are also very grateful for the forebearance and co-operation of all of the patients and control subjects in this study. A. J. T. is funded by the Wellcome Trust.

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Received 19 October 1994; revised 17 January 1995; accepted for publication 17 January 1995