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 profound consumption coagulopathy and progressive systemic neurovascular 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 A2 neurotoxin which inhibits the release of acetylcholine from presynaptic cholinergic nerve terminals (KAMENSKAYA & THESELEFF, 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).

(iii) Calculation of sensory nerve conduction velocities.

Repetitive nerve stimulation studies (RNS).
(i) Recording the change in CMAP amplitude recorded in abductor digitii 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 of abductor pollicis and abductor digitii 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 digitii 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 digitii 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 of age and height matched for comparison of the amplitudes.

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...
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).

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

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<th>No.</th>
<th>Mean change (%)</th>
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<tr>
<td>Controls</td>
<td>22</td>
<td>104.2 (102.5–105.9)</td>
</tr>
<tr>
<td>Envenomed patients (stage 4/5)</td>
<td>16</td>
<td>92.5 (88.5–96.5)</td>
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*95% confidence intervals in parentheses.

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. i. 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.

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

<table>
<thead>
<tr>
<th></th>
<th>Ratio of 9th to 1st post-tetanic value (%)</th>
<th>Ratio of 1st post-tetanic to 1st pre-tetanic value (%)</th>
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<tbody>
<tr>
<td>Controls</td>
<td>151 (106–108)</td>
<td>303</td>
</tr>
<tr>
<td>Envenomed patients (stage 4/5)</td>
<td>9 (51–81)</td>
<td>174</td>
</tr>
</tbody>
</table>

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-
References


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