Electrocardiographic abnormalities in patients bitten by taipans (*Oxyuranus scutellatus canni*) and other elapid snakes in Papua New Guinea

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Abstract

Envenoming by a number of species of snake may affect the myocardium or cause electrocardiographic changes; several different mechanisms have been proposed. In a prospective study of snake bite in Papua New Guinea, electrocardiographic changes were observed in 36 of 69 patients (52%) envenomed by the taipan (*Oxyuranus scutellatus*), 2 of 6 (33%) envenomed by death adders (*Acanthophis* sp.) and one envenomed by the brown snake (*Pseudonaja textilis*). Septal T wave inversion and bradycardias, including atrioventricular block, were the commonest abnormalities. There was no haemodynamic deterioration. The cause of these changes is uncertain; only 2 of 24 patients (8·3%) with electrocardiographic changes had markedly elevated plasma concentrations of cardiac troponin T, a sensitive and specific marker of myocardial damage. This suggests that myocardial damage is uncommon following bites by these species. Electrocardiographic abnormalities are most likely to have been caused by a direct toxic effect of a venom component upon cardiac myocyte function; in taipan bites, taicatoxin, a calcium channel blocker, might be responsible.

Keywords: snake bite, *Oxyuranus scutellatus canni*, *Acanthophis* sp., *Pseudonaja textilis*, electrocardiography, Papua New Guinea

Introduction

Electrocardiographic abnormalities or involvement of the myocardium has been observed following envenoming by a number of different species of snake. The mechanism of myocardial involvement varies considerably between species. Despite the presence of venom components which might affect the heart, electrocardiographic changes have been reported rarely in Australasian elapid envenoming; in the pioneering studies of Campbell on snake bite in Papua New Guinea, electrocardiographic changes were not observed and clinical evidence of myocardial involvement was rare (CAMPBELL, 1967a, 1967b). More recent observations (B. Currie, personal communication) suggested that electrocardiographic changes were more common than originally suspected following bites by the taipan (*Oxyuranus scutellatus canni*). As part of a large prospective study of snake bite, we performed electrocardiography and looked for evidence of myocardial damage in patients presenting with envenoming following a snake bite.

Patients and Methods

All patients presenting with a history of snake bite to Port Moresby General Hospital (PMGH) in Papua New Guinea between March 1990 and June 1992 were studied prospectively. History and examination were recorded on standard forms. Blood was taken for biochemical investigations and 2mL of whole blood were placed in a new, clean, dry, glass tube for determination of the 20 min whole blood clotting test (20 WBCT) (WARRELL *et al.*, 1977; SANO-MARTINS *et al.*, 1994). Serum and urine samples and bite wound swabs and aspirates were frozen at –70°C for venom detection. Electrocardiograms (ECGs) were performed as soon after admission as possible in a proportion of patients with envenoming. Patients with signs of envenoming (local lymph node tenderness, incoagulable blood or neurotoxicity) were treated with one ampoule of polyspecific antivenom (Commonwealth Serum Laboratories, Melbourne, Australia) 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 every 6 h for the first 36 h and daily thereafter. Biochemical investigations were repeated 24 h later. In a small subgroup of patients, repeat ECGs were obtained during admission.

Laboratory methods

ECGs were included in the analysis if a clear diagnosis of the biting species had been made by detection of venom antigen in admission samples (THEAKSTON *et al.*, 1977; HO *et al.*, 1986; LALLOO *et al.*, 1994). Total creatinine kinase (CK) activities were measured in Port Moresby using a Technicon RA-1000™ or Technicon RA-XT™ autoanalyser. Cardiac troponin T (cTnT) concentration was measured in plasma which had been stored frozen at –70°C and transported on dry ice to England (UK). Samples were assayed at the Royal Brompton Hospital, London, in a single-step sandwich assay using the Boehringer Mannheim enzyme-linked immunosorbent assay Troponin-T™ kit (Boehringer Mannheim, UK) on the Boehringer Mannheim ES 300™ immunoassay analyser.

Statistics

The relationship of clinical categories to the presence of an abnormal ECG was assessed using a χ^2 test with Yates's correction. Continuous variables were compared between groups using the non-parametric Mann–Whitney *U* test.

Results

Clinical features of envenoming by the taipan and death adder have been reported previously (LALLOO *et al.*, 1995, 1996). ECGs from 76 envenomed patients with an enzyme immunoassay proven diagnosis were analysed; abnormalities were present in 36 of 69 patients (52%) envenomed by taipans (*O. scutellatus*), 2 of 6 patients (33%) envenomed by death adders (*Acanthophis* sp.) and one envenomed by a brown snake (*Pseudonaja textilis*). Two major patterns of ECG changes were seen: T wave inversion and bradycardias or atrioventricular block. In some patients both were present (Table). T wave inversion was most commonly seen in the septal region and was frequently deep and symmetrical; in some patients all of the anterior leads were involved. Sinus bradycardia was the commonest rhythm abnormality, although first, second and third degree atrioventricular block were seen. In 5 patients there were obvious J waves, and in another 7 patients there were small deflections consistent with J waves. QTc intervals were at the upper limit of normal compared to published Caucasian values (FISCH, 1992) in most patients, irrespective of whether the ECG was normal or

abnormal. The time course of ECG changes was studied in only a few patients. ECG changes were usually present on admission, although they were occasionally first noted over 24 h after the bite. In most patients with bradycardia, ventricular rates started to return to normal between one and 3 d after admission. T wave changes took longer to resolve; the depth of T wave inversion tended to start to resolve 3–4 d after the bite, but abnormalities were present for up to a week. The Figure shows ECGs from a patient admitted 23 h after a bite by a taipan; administration of antivenom resulted in a return to normal of initially inverted T waves. However, 12 h after admission septal T wave inversion had returned and this persisted for several days. Haemodynamic dysfunction was rare; no significant episode of hypotension was observed and there was no association between blood pressure levels and the presence or absence of ECG abnormalities. Severe electrolyte disturbance did not occur in any patient.

Comparisons made in the large group of patients bitten by taipans showed no association between the presence of coagulopathy and an abnormal ECG, but there was a trend towards an association between the severity of envenoming (measured by the need for intubation) and an abnormal ECG (Yates's corrected $\chi^2=2{\cdot}85$, $P=0{\cdot}09$). Total CK activity was raised to more than twice the upper limit of normal in 49% of 51 taipan bite patients tested, but there was no relationship between the peak CK activity and the presence or absence of ECG abnormalities.

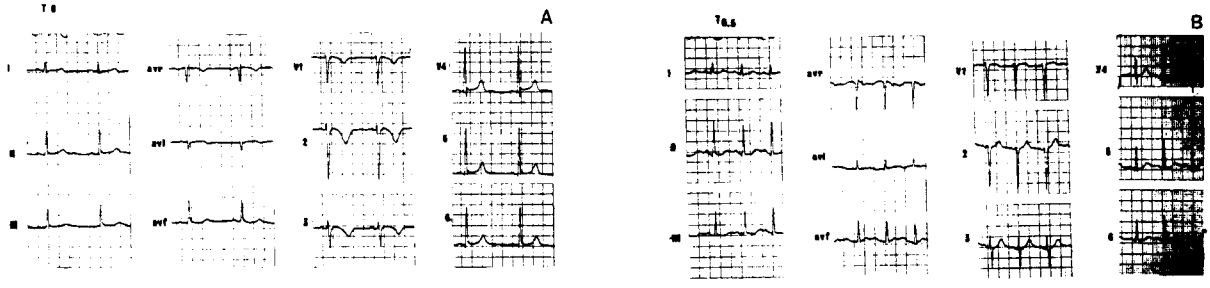

Figure. T wave changes in a patient bitten by a taipan. (A) On admission, (B) 30 min later following antivenom administration.

Table. Electrocardiographic findings in 76 patients envenomed by elapid snakes

Taipan[a]	69
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/1st degree atrioventricular block	2 (2·9%)
Bradycardia/left bundle branch block	1 (1·4%)
Intraventricular conduction defect	2 (2·9%)
Complete heart block	1 (1·4%)
Atrial arrythmias	2 (2·9%)
Frequent ventricular ectopics	1 (1·4%)
Death adder	6
Normal	3 (50·0%)
2nd degree atrioventricular block (type II)	1 (16·7%)
Septal T wave inversion	1 (16·7%)
Eastern brown snake	1
Septal T wave inversion	1

[a]4 patients had T wave changes and a sinus bradycardia, 2 patients had T wave changes and 1st degree atrioventricular block, one patient had T wave changes and an intraventricular conduction defect.

Plasma cTnT concentrations were markedly elevated in only 3 of 39 patients (7·7%) tested both at the time of admission and approximately 24 h after the bite: 2 of 24 patients (8·3%) with ECG changes and 1 of 15 (6·7%) without such changes. The median concentration of cTnT was <0·1 μg/L in both groups ($P=0{\cdot}25$; reference range <0·1 μg/L). Elevated concentrations were seen in one patient bitten by a death adder, who developed second degree heart block (peak CK activity 4220 units/L, cTnT concentration 2·7 μg/L) and in one patient bitten by a taipan, who had a bradycardia of 43 beats/min, a prolonged QTc interval of 0·45 s, and marked septal T wave inversion in leads 1–3 (peak levels: CK=213 units/L, cTnT=1·1 μg/L). One patient with no ECG abnormality had a cTnT concentration of 1·0 μg/L. In acute myocardial infarction, mean cTnT concentrations of up to 9·2 μg/L are reached within the first 24 h (WU *et al.*, 1994).

Discussion

These results showed a much higher frequency of ECG changes following bites by elapid snakes in Papua New Guinea than suggested by the sole Australian case report of QRS complex widening following envenoming by the eastern brown snake (*Pseudonaja textilis*) (BUCKLEY & DAWSON, 1993). Despite their frequency, these changes were rarely of clinical significance, although in a small number of cases the observed dysrhythmias were potentially life threatening. Electrocardiographic abnormality or involvement of the myocardium has been observed following envenoming by a number of different species of snake including *Vipera berus* (see REID, 1976), *Atractaspis engaddensis* (see ALKAN & SUKENIK, 1975), *Echis ocellatus* (see WARRELL *et al.*, 1977) and *Calloselasma rhodostoma* (see REID *et al.*, 1963). Various mechanisms have been suggested: directly acting 'cardiotoxins' (NAYLER *et al.*, 1976), myotoxins causing cardiac muscle damage (ROWLANDS *et al.*, 1969), coronary vasospasm or thrombosis (WOLLBERG *et al.*, 1988; TIBBALLS *et al.*, 1992), myocardial haemorrhage (THAN-THAN *et al.*, 1989), electrolyte disturbances (REID, 1961), and severe hypotension (MYINT-LWIN *et al.*, 1985).

The explanation for the abnormalities observed in our patients is uncertain and might have varied among the 3 species of snake involved. Myocardial damage has been reported in a victim of one species of Australian elapid, the king brown snake *Pseudechis australis*; small foci of myocardial damage and massive skeletal rhabdomyolysis were seen in a fatal case (ROWLANDS *et al.*, 1969) and a specific toxin, 'mulgotoxin,' which causes cardiovascular depression in rats, has been isolated from the venom (S. L. Geh & R. M. Rampal, unpublished observations). The effect of the myotoxic phospholipase A2, taipoxin, on cardiac muscle cells is not known, but the rarity of elevated levels of plasma cTnT appears to exclude myocardial damage as a cause of the observed ECG changes in most patients. However, the observation that the highest level of cTnT was seen in the patient bitten by a death adder, who had one of the most profound ECG abnormalities, suggests that, in envenoming by some species, ECG changes may be due to cardiac muscle damage. Death

adder venom is not known to contain an obvious cardiotoxic component, although biochemical evidence of myotoxicity has recently been described in patients bitten by this species and some samples of *Acanthophis antarcticus* venom contain phospholipase A activity (LALLOO *et al.*, 1996).

Venom components could also affect the coronary circulation. In experimental eastern brown snake (*Pseudonaja textilis*) envenoming in dogs, hypotension, ST elevation and T wave inversion occurred following the intravenous infusion of whole venom or the purified prothrombin activator (TIBBALLS *et al.*, 1989, 1992). Heparin pretreatment abolished these changes and myocardial depression was thought to be secondary to disseminated intravascular coagulation; the presence of microscopic thrombi within the pulmonary circulation and in the coronary artery in one animal at post-mortem suggested that obstruction to coronary flow could cause ECG changes (TIBBALLS *et al.*, 1989, 1992). In patients bitten by taipans and eastern brown snakes, ECG changes might reflect cardiac ischaemia secondary to coronary artery obstruction. However, the absence of cardiac muscle damage and the particular pattern of T wave changes in the septal region make this an unlikely explanation. Reduced coronary perfusion due to hypotension was not the cause of ECG changes in our patients.

ECG changes might be attributable to disturbances of the autonomic innervation of the heart. Unilateral alteration of sympathetic tone is associated with ECG abnormalities (YANOWITZ *et al.*, 1966), and in the long QT syndrome, which is frequently associated with T wave changes, abnormal cardiac innervation occurs affecting conduction and repolarization within the heart (ESLER, 1992). ST and T wave changes occurring following subarachnoid haemorrhage have been attributed to disturbance of autonomic innervation (YAMOUR *et al.*, 1980). We found no evidence of autonomic disturbance in any case, although formal autonomic testing is very difficult in intubated and ventilated patients. It seems most likely that the ECG changes were due to a direct toxic effect of a venom component, either on the heart or on the innervation of the heart. There is circumstantial evidence to support this. QTc intervals in patients were at the upper limit of normal or slightly prolonged, compared with published Caucasian normal ranges; this is consistent with venom components affecting autonomic function, but could also occur if repolarization were directly affected by a toxin. The finding of J waves in some patients, thought to be a manifestation of an increased voltage gradient between epicardial and endocardial cells (ANTZELEVITCH *et al.*, 1991), might also suggest that certain membrane channels are being directly affected by the venom. In particular, the ECGs of the patient shown in the Figure, in which T wave changes present on admission disappeared 30 min after antivenom was given and then recurred 12 h later, suggest a direct toxic effect. However, our understanding of this process remains incomplete and more work is required before all of the observed ECG findings can be fully explained.

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Further information can be obtained from Dr Stephen Hicks, Department of Biological Sciences, University of Warwick, Coventry, CV7 4AL, UK; phone +44 (0)1203 523540, fax +44 (0)1203 523701, e-mail wupert@dna.bio.warwick.ac.uk