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The efficacy of antivenom in the treatment of bites by the Papuan taipan (*Oxyuranus scutellatus canni*)

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Abstract

A prospective series of 156 patients systemically envenomed following the bite of a Papuan taipan (*Oxyuranus scutellatus canni*) were studied. All patients were treated with appropriate antivenom and clinical course and outcome were compared. The proportion of patients requiring intubation was significantly smaller, and the time to resolution of neurotoxicity and discharge from hospital significantly shorter, in patients receiving antivenom no more than 4 h after the bite. No significant difference in outcome was demonstrated between patients receiving antivenom at various times after 4 h. No difference was demonstrated in the times to restoration of coagulability between the 2 groups. The only significant difference between a small number of patients given 2 vials of antivenom and patients given a single vial at the same time after envenoming was a marginally shorter duration of intubation in those who required it. The study suggests that, to achieve significant clinical benefit in Papuan taipan bite, antivenom must be given as early as possible.

Keywords: snake bite, *Oxyuranus scutellatus*, treatment, Papua New Guinea

Introduction

Each year, about 90 patients are admitted to Port Moresby General Hospital (PMGH) in Central Province, Papua New Guinea (PNG), with systemic envenoming following a snake bite. Most of these (89% in the last 3 years) have been bitten by a Papuan taipan (*Oxyuranus scutellatus canni*). Taipan venom contains a number of toxins including a prothrombin activator, pre- and post-synaptic neurotoxins, and a calcium channel blocker. The main clinical features of envenoming are local lymphadenopathy, coagulopathy, systemic spontaneous bleeding, and progressive neurotoxicity involving ophthalmic, bulbar and peripheral musculature. This often involves respiratory muscles and up to 50% of patients require mechanical ventilation which, in Central Province, can by performed only at PMGH. Antivenom is the mainstay of treatment for patients envenomed by the Papuan taipan. Both polyspecific and monospecific taipan antivenoms are available, produced by Commonwealth Serum Laboratories, Melbourne, Australia, by hyperimmunization of horses using the venom of the related Australian taipan (*O.s. scutellatus*). Both antivenoms contain 12 000 units of taipan antivenom. The PNG department of health spends over £100 000 a year on antivenom, most of which is used to treat patients who have been bitten by taipans in Central Province. Many patients are bitten in remote parts of the Province and do not receive antivenom until several hours after the bite, by which time they have haemostatic disturbance and established neurotoxicity. *In vitro* evidence suggests that, once presynaptic neurotoxins have bound to the nerve terminal, the process is irreversible (FOHLMAN *et al.*, 1976; SU & CHANG, 1984). We have analysed the relationship between the time of administration of antivenom and the clinical outcome.

Methods

Between May 1990 and May 1993, all patients admitted to PMGH with unequivocal signs of systemic envenoming following a snake bite were entered into a prospective clinical study. Patient details were recorded on a standard proforma. Observations were made at least every 6 h for the first 24 h after admission and every 12 h thereafter until discharge. Patients were managed according to standard treatment protocols, receiving one vial of antivenom. Polyspecific antivenom was given unless the biting species was known. A few patients received 2 vials of antivenom. Antivenom was given as soon as possible after the time of envenoming, either at a health centre or on admission to PMGH. Patients were intubated if they had evidence of bulbar paralysis with significant pooling of secretions and were mechanically ventilated using a Bird mark 7 pressure cycled ventilator if they had clinical evidence of impaired respiratory function (falling tidal volume and minute volume, decreasing respiratory excursion, increasing respiratory rate). Intravenous opiates and benzodiazepines were given as required for sedation. Neuromuscular blocking agents were not used. Patients were weaned from the ventilator when they were able to maintain an adequate tidal volume (judged clinically), had a respiratory rate of less than 25/min, could cough and clear secretions effectively, sustain hand grip, and maintain head lift for a minimum of 5 sec. They were extubated if adequate respiratory function was maintained.

All patients had a serum sample taken at admission. When a bite site could be identified, a wet cotton wool swab was used to wipe the site and an aspirate of the bite site was taken by infusing and aspirating 0·5 mL of 0·5% lignocaine along the fang marks. When possible 5 mL of urine were collected at admission. Samples were stored at −70°C and subsequently tested for the presence of venom antigen of the Papuan taipan (*O. scutellatus canni*), the Papuan black snake (*Pseudechis papuanus*), the death adder (*Acanthopis* spp.) the eastern brown snake (*Pseudonaja textilis*), and the small-eyed snake (*Micropechis ikaheka*) at the Liverpool School of Tropical Medicine, UK (THEAKSTON *et al.*, 1977; HO *et al.*, 1986). At admission, 2 mL of blood were put in a clean, new, glass tube. After 20 min the presence or absence of a blood clot was noted (WARRELL *et al.*, 1977). With some of the patients with non-clotting blood, the test was repeated sequentially and the time at which samples began to clot noted.

During admission, specific events were noted, including: time of bite, time of admission, time of receiving antivenom, time and length of intubation and ventilation, and time to discharge. The time to complete resolution of ophthalmoplegia was estimated as the mid-point between observations when eye movements unequivocally were and were not limited. Definitive taipan bites were identified in one of two ways: (i) the retrospective demonstration of taipan venom antigen in at least one of: admission serum, bite site swab, aspirate or urine sample; and (ii) identification of a dead snake killed and brought with the patient.

Patients were grouped according to the time elapsing between the bite and receiving antivenom.

Statistics. All data were stored and analysed in databases created using the Epi-Info® package (USD) and the

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Instat® biostatistics program (GraphPad® software). The χ^2 test was used to compare non-categorical variables. All non-normally distributed continuous variables were analysed using the Kruskal–Wallis ranked correlation test.

Results

One hundred and fifty-six patients were identified who were admitted to PMGH with signs of systemic envenoming following the bite of a taipan; 109 received a single vial of polyspecific antivenom, 32 received a single vial of taipan monospecific antivenom, 11 received 2 vials of polyspecific antivenom, 3 received 2 vials of taipan antivenom, one received one vial of polyspecific and one vial of taipan antivenoms. The median time after the bite at which appropriate antivenom was given was 5·25 h. Four patients were initially given antivenom inappropriate to the retrospectively identified biting species at a health centre but subsequently received appropriate antivenom on arrival at PMGH. There is no evidence of any cross protection between antivenoms from different species (SUTHERLAND, 1983) and these patients were grouped according to the time after envenoming at which they received appropriate antivenom.

Survival and intubation

The numbers of patients given antivenom at various times after envenoming and the proportion who subsequently developed neurotoxicity of sufficient severity to require intubation are shown in Table 1. The number of surviving patients in each group is also shown.

Table 1. The proportions of patients given antivenom at various times after envenoming requiring intubation, and their survival

Time between bite and antivenom administration (h)	No. of patients	No. intubated	No. surviving
0–2	18	6 (33%)	18
2–4	42	9 (21%)	42
4–6	24	16 (66%)	24
6–8	19	12 (63%)	19
8–12	14	8 (57%)	12
>12	24	17 (71%)	23
5·25[a]	15	9 (60%)	15

[a]Patients received 2 vials of antivenom; time shown is the median time to administration of the first vial.

The mean time after envenoming at which antivenom was given to patients who subsequently required intubation was 10·2 h; it was 5·8 h in those who did not ($P<0·0001$, Kruskal–Wallis test).

The mean duration of admission, intubation and time to neuroresolution in the various groups divided on the basis of time of receiving antivenom are shown in Table 2. Similar data are shown from 15 patients who received 2 vials of appropriate antivenom.

One hundred and twenty-nine patients had incoagulable blood at admission. Samples were taken from 72 of them every 6 h until the blood clotted. Results from patients who received only a single vial are shown in Table 3. The mean time after envenoming at which antivenom was given was 2·8 h in the early group and 11·4 in the late group. No further stratification was attempted because of the small numbers and the imprecision of the end point. All significant bleeding episodes occurred within the first few hours after envenoming. Eighty-six patients (55%) had spontaneous bleeding before or on admission to hospital, most commonly from gums, the wound site, cuts, and venepuncture sites. Thirteen patients had minor haematemeses or haemoptyses, and one patient had a suspected intracerebral bleed. No patient developed a significant new bleeding episode after admission to hospital.

Deaths

There were 3 deaths in the series. One patient died of respiratory arrest on arrival at the hospital 46·5 h after the time of the bite, after delayed referral. One patient died suddenly during the night while being ventilated. The third death was the unexpected sudden death during convalescence of an old man who also had pulmonary tuberculosis.

Clinical sequelae

Seventy-six patients attended for follow-up one to 2 weeks after discharge. The only common sequel was persistant loss of sensation around the bite site. No difference was detected between patients who received early and late antivenom.

Discussion

The study showed that a single vial of polyspecific or monospecific taipan antivenom given within 4 h of envenoming benefits victims of Papuan taipan bite, when compared to treatment given later. A smaller proportion of patients who received antivenom at or before 4 h required intubation (22·4% vs. 68·1%, $P<0·002$, χ^2 test). The mean duration of hospital stay (4·6 d vs. 7·1 d, $P<0·0001$, Kruskal–Wallis test) and the mean time to resolution of neurotoxicity (52·4 h vs. 107·5 h, $P<0·0001$, Kruskal–Wallis test) were both reduced. The relative risk of requiring intubation in patients receiving antivenom more than 4 h after envenoming was 2·62. There was no significant difference in outcome between patients given antivenom at various times before, or at various times after, 4 h. Patients who were given 2 vials of appropriate antivenom, the first at a median time of 5·25 h, had a marginally better neurological outcome than those patients who received a single vial between 4 and 6 h after envenoming, with a shorter duration of intubation required ($P<0·01$), but there was no significant difference in the proportion requiring intubation, the length of admission, or the time to complete neuroresolution.

Table 2. Duration of admission, intubation and time to complete resolution of ophthalmic signs of neurotoxicity in patients given antivenom at various times after snake bite

Time between bite and antivenom administration (h)	No. of patients	Duration of admission (d)[a]	Duration of intubation (h)[a]	Time to neuroresolution (h)[a]
0–2	18	4·8±1·7 (3)	101±22·4 (93)	60±26·5 (73)
2–4	42	4·2±1·0 (4)	77±12·8 (74)	55±13·0 (45)
4–6	24	8·0±1·8 (7·5)	111±13·9 (107)	113±9·9 (114)
6–8	19	6·6±1·1 (6·5)	83±15·7 (86)	106±9·8 (96)
8–12	14	6·5±1·2 (5·5)	117±34·2 (94)	101±11·7 (95)
>12	24	7·3±1·6 (6·5)	87±22·0 (79)	105±17·7 (99)
5·25[b]	15	6·7±1·5 (5·5)	75±15·9 (75)	106±9·0 (96)

[a]Means ±2×standard error of the mean (median values in parentheses).
[b]Patients received 2 vials of antivenom; time shown is the median time to administration of the first vial.

Table 3. Time to antivenom administration and [illegible] coagulability

Time to antivenom administration (h)	No. of patients	Percentage with coagulable blood after times shown				
		6 h	12 h	18 h	24 h	
≤4	33	36·4	75·8	91	97	
>4	31	51·6	87·1	100	–	

The number of patients for whom estimations of time of clotting were made was too small to allow any firm conclusion to be drawn. There was, however, no significant difference in the proportion of patients with coagulable blood at 6, 12 and 18 h between the early and late antivenom groups. The onset of coagulopathy in envenomed patients typically occurred within 2 h of the bite and one vial of antivenom given after this did not appear to speed resolution. LALLOO (1994) found that the rate of recovery of fibrinogen levels and clotting times was no faster in 5 patients given 2 vials of antivenom than in those given one vial, but the numbers in our study were too small to add to that finding.

The purpose of giving antivenom in the management of snake bite is to diminish morbidity and mortality and speed recovery from envenoming. It is, however, extremely difficult to assess how effective antivenom is in achieving these aims. No 2 victims of snake bite are directly comparable. Since its introduction in 1962, antivenom has become an integral part of the management of victims of Australian and Papuan taipan bite and it has been suggested that, before the introduction of antivenom, envenoming by the taipan was almost invariably fatal (SUTHERLAND, 1983). Antivenom should be given as soon as possible after envenoming, but is there a time beyond which it ceases to be useful? It has been suggested that 'it is never too late to give antivenom' (MINTON, 1974; SUTHERLAND, 1977), but is this true? The recommended initial dose of taipan antivenom is 12 000 units, the amount contained in one vial of both monospecific and polyspecific antivenom. This is the dose required to neutralize the amount of venom yielded on average by 'milking' an Australian taipan (SUTHERLAND, 1983). Some patients may need much higher, repeated doses (SUTHERLAND, 1976), but it is not clear how to identify them, how much antivenom should be given, and whether there is a time beyond which additional antivenom is of no benefit.

Antivenom is extremely expensive for PNG to buy from a limited drug budget. A single vial of polyspecific antivenom costs £595. It is always in short supply and is sometimes not available. It is also potentially dangerous, the risk of significant side effects increasing as higher doses of the drug are given. It is important therefore that it is used selectively and to maximum benefit, both for the individual patient and for the community as a whole. Multiple doses cannot be recommended unless we can be sure that they benefit the patient.

It has been shown *in vitro* that taipoxin, the principal pre-synaptic neurotoxin in taipan venom, causes an irreversible block of neuromuscular transmission after a latent period (FOHLMAN *et al.*, 1976). Binding is poorly reversible and, *in vitro*, bound toxin rapidly becomes inaccessible to neutralizing antibody (SIMPSON *et al.*, 1993). Addition of antivenom or washing the nerve–muscle preparation after binding had occurred did not prevent or reduce neuromuscular blockade (SU & CHANG, 1984). It seems likely that a similar situation obtains in patients. For antivenom to prevent neurotoxicity it must be given before the neurotoxins have bound to the nerve terminal. Similarly, the prothrombin activator in taipan venom causes a consumption coagulopathy. Most patients in this series who developed coagulopathy had incoagulable blood within 2 h of the bite, in keeping with the observations of CURRIE *et al.* (1992). It is likely that patients with a propensity to bleed do so at this time, which may explain why few patients in our experience developed significant bleeding after admission to hospital. Antivenom given after coagulopathy is established may neutralize remaining circulating toxin components and speed recovery, but its effect in diminishing the risk of bleeding may be limited.

No-one would countenance withholding antivenom from a patient who might benefit from it. It is impossible to say, however, whether there is a time beyond which antivenom ceases to produce a significant benefit, which means that clinicians must give antivenom to envenomed patients, no matter what the time of presentation. Analysis of the outcome of patients in this series suggests several points of practical importance for the treatment of snake bite victims in PNG. In order for patients to be treated quickly, at least one strategic health centre distant from PMGH in both the east and west of Central Province must have supplies of appropriate antivenom (and a reliable refrigerator to keep it in) at all times. 76% of patients in this series reached a health facility, but only 48% received antivenom, within 4 h of the bite, either because antivenom was not available or because of avoidable delay in instituting treatment. The need to regard antivenom therapy as emergency treatment must be reemphasized. The use of pressure immobilization bandages is recommended as first aid treatment in PNG (SUTHERLAND, 1985), but despite active education measures they are still rarely used and this message must be reinforced. An effective pressure bandage may, by delaying the absorption of venom, increase the time period in which antivenom produces maximum benefit. Administration of the incorrect type of antivenom is largely avoidable in PNG. Black snake bites are extremely rare in Central Province. The distinction clinically between a taipan bite and a black snake bite is virtually impossible and, if black snake bite is considered a possibility, polyspecific antivenom must be given. The possible role of venom detection kits is discussed elsewhere (TREVETT *et al.*, in press). The widescale use of larger volumes of antivenom in PNG is unlikely in the near future because of its expense, limited supplies and unproven benefit.

The numbers of patients in the various groups in this study were small. There are potential errors both in drawing comparisons between different snake bite victims and in calculating the end points chosen for analysis. For the majority of the patients in this series, antivenom treatment did not achieve its goal and, for most patients, that may have been because it was given too late. In the future, new antivenoms produced specifically against Papuan taipan (*O. scutellatus canni*) venom or against subunits of the individual toxins may prove more effective than existing antivenom, but neutralization of toxins before they have bound remains the optimal strategy.

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Announcements

Second Seminar on Food-borne Parasitic Zoonoses: Current Problems, Epidemiology, Food Safety and Control
Khon Kaen, Thailand, 6–9 December 1995

The SEAMEO TROPMED PROJECT is organizing a Second Seminar on Food-borne Parasitic Zoonoses to be held in Khon Kaen, Thailand, on 6–9 December 1995. In addition to scientific sessions a one day trip will be made into Laos. Additional information can be obtained from the SEAMEO TROPMED PROJECT, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand or from Dr John H. Cross, Uniformed Services University of The Health Sciences, Bethesda, MD 20814, USA. Telephone +1 (301) 295-3139; Fax +1 (301) 295-1971.

Annual International Course on Identification of Insects and other Arthropods of Medical and Veterinary Importance
3–21 July 1995
The Natural History Museum, London, UK

This course leads to the acquisition of an NHM Short Course Diploma. The course fee is £1400, excluding accommodation which can be arranged for an additional £700.

Further information and application forms can be obtained from Mrs C. A. Lowry, The Natural History Museum, Medical and Veterinary Division, Department of Entomology, Cromwell Road, London, SW7 5BD, UK; telephone +44 171 938 9125/9329, fax +44 171 938 9395/8937.

First European Conference on Tropical Medicine
Hamburg, Germany
22–26 October 1995

This meeting will include the formation of the European Federation of Societies of Tropical Medicine, in which the Royal Society of Tropical Medicine and Hygiene will participate.

Further information on the scientific programme can be obtained from the Congress Secretariat, Bernhardt Nocht Institute for Tropical Medicine, Bernhardt-Nocht-Strasse 74, D-20359 Hamburg, Germany (phone +49 (0) 40 31 18 25 11, fax +49 (0) 40 31 18 25 12). Registration forms can be obtained from the Congress Secretariat, Congress Centrum Hamburg Congress Organization, Jungiusstrasse 13, PO Box 30 24 80, D-20355 Hamburg, Germany (phone +49 (0) 40 35 69 22 45, fax +49 (0) 40 35 69 23 43). The date for submission of abstracts is 30 June 1995.