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Antivenom use, premedication and early adverse reactions in the management of snake bites in rural Papua New Guinea

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Abstract

Objective: To examine antivenom use, premedication, early adverse reactions and patient outcomes after snake bite in rural Papua New Guinea.
Design: Retrospective chart analysis of all admissions for snake bite with documented antivenom use at 11 rural health facilities from January 1994 to June 2004. No formal protocol was followed and there was no attempt at randomisation or blinding of prophylaxis.
Results: Antivenom use was documented in 136/1881 (7.2%) snake bite admissions and most (121/136: 88.9%) received a single vial. CSL Polyvalent antivenom was administered to 112/136 (82.4%). One hundred and eleven patients (81.6%) happened to have been given premedication with adrenaline and/or promethazine and/or hydrocortisone. Early adverse reactions were reported in 25 patients (18.4%) including 23 treated with polyvalent antivenom. Intravenous test doses of antivenom were given to 32 patients, none of whom had a positive test result. Subsequent adverse reactions occurred in 9 of these 32 (28.1%) patients. One death may have been attributable to anaphylaxis after polyvalent antivenom. Reaction rates were significantly ($p \leqslant 0.005$) lower in adrenaline premedicated patients (7.7%) compared to patients premedicated without adrenaline (28.3%) and unpremedicated patients (28.0%). Adrenaline premedication caused no detectable changes in vital signs. The case fatality rate was 9.6% (13/136 patients).
Conclusions: Polyvalent antivenom is the main treatment for envenomation in rural health centres, and early adverse reactions are common. Adrenaline premedication appears to significantly reduce acute adverse reaction rates. Premedication with promethazine and/or hydrocortisone without adrenaline did not reduce early adverse reactions.

Keywords: Snakebite; Adrenaline; Premedication; Papua New Guinea; Anaphylaxis; Drug reactions

1. Introduction

Antivenom is the most effective treatment for snake bite envenomation, but the use of such immunoglobulins is not without risk (Sutherland

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and Tibballs, 2001; Ariaratnam et al., 2001; Smalligan et al., 2004). Early adverse reactions, including fatal anaphylaxis, are known complications (Sutherland, 1977; Warrell et al., 1977; Corrigan et al., 1978; Sutherland and Lovering, 1979; Malasit et al., 1986; Warrell et al., 1986; Sutherland, 1992; Moran et al., 1998). As a result, prophylactic treatment with combinations of adrenaline, antihistamines and/or corticosteroids has been recommended for prevention of antivenom reactions since the 1960s (Trinca, 1963; Sutherland, 1976; Tibballs, 1994; Sutherland and Tibballs, 2001), but only recently have these practices been the subject of clinical trials (Fan et al., 1999; Premawardhena et al., 1999; Gawarammana et al., 2004).

Studies of the efficacy and safety of premedication strategies have been conducted in Sri Lanka (Premawardhena et al., 1999; Gawarammana et al., 2004) and in Brazil (Fan et al., 1999). A prospective study of subcutaneous adrenaline premedication in Sri Lanka claimed a statistically significant reduction in the incidence and severity of early reactions to Indian polyvalent snake antivenom (Premawardhena et al., 1999), but was criticised as being underpowered after being halted prematurely (Ball and Tisocki, 1999). A study of hydrocortisone use (with or without chlorpheniramine) in Sri Lanka reported a reduction in adverse reactions but was also underpowered and the result statistically insignificant (Gawarammana et al., 2004). An earlier trial of promethazine reported no difference in reaction rates between patients treated with antihistamine and those treated with a placebo as premedication for Brazilian snake antivenom (Fan et al., 1999). Debate over the relevance of antivenom premedication in modern emergency departments and intensive care facilities (Tibballs, 1994; White, 1998; Currie, 2000; Cheng and Winkel, 2004) ignores the fact that the burden of snake bite management mostly falls on under-resourced rural health clinics in tropical developing countries where there are few doctors and minimal resuscitation facilities (Lalloo et al., 1995; Chippaux, 1998; Cheng and Winkel, 2001b; Williams, 2005).

Papua New Guinea (PNG) is one such tropical developing country; the regional incidence of snake bite in this pacific nation is among the highest in the world (Williams, 2005) while the doctor-patient ratio is among the lowest (Naraqi et al, 2003). Historically, Commonwealth Serum Laboratories (CSL) polyvalent antivenom has been associated with adverse reaction rates of up to 54% in Papua New Guinea (Campbell, 1964, 1967, 1969; Brian and Vince, 1987; Hudson and Pomat, 1988) but there are few reports from Australia (Sutherland, 1992, Sutherland and Lovering, 1979). One study associated lower antivenom reaction rates with combination premedication using promethazine and hydrocortisone rather than to giving promethazine alone (Brian and Vince, 1987) but no detailed analysis of adverse antivenom reactions in PNG has ever been published.

To obtain information on the current antivenom use, and the outcomes of antivenom premedication in rural PNG health centres, we undertook a retrospective audit of 10 years of snake bite management in southern PNG. Analysis provides useful new data on early adverse reaction rates to CSL antivenoms, and current usage practices in rural PNG. The results could help the design of randomised clinical trials (RCTs) of premedication efficacy in PNG, and the rationalisation of current treatment protocols.

2. Materials and methods

2.1. Ethics

Ethics approval was obtained from both the PNG Medical Research Advisory Committee (MRAC No. 01.09/2001) and James Cook University's Human Ethics Sub-Committee (H1239/2001).

2.2. Patients

A database containing complete case notes from 1881 snakebite patients admitted to 11 rural health centres in Central, Gulf and Western provinces of Papua New Guinea between 1 January 1994 and 30 June 2004 was examined and 136 file records in which antivenom use was documented were identified.

2.3. Quality of medical records

Rural health centres use standard patient observation sheets to record vital signs and clinical signs at 15–30 min intervals. Medical records which lacked sufficient detail were excluded.

2.4. Locations

Medical records were from 11 rural health centres or hospitals at Bereina, Inauaia, Kwikila, Moreguina, Veifa'a (Central province); Malalaua, Kikori (Gulf province); Balimo, Daru, Rumginae and Wipim (Western province). These are major primary and secondary facilities responsible for large patient catchments across southern PNG.

2.5. Data examined

Details of type, quantity, method and time of administration of antivenom; type, quantity, method and time of administration of any premedicating drugs; patient age and sex; time of snakebite; vital signs and adverse reactions were extracted from patient records and the information recorded directly in a Microsoft Excel® spreadsheet for analysis. Interobserver bias was avoided by having a single knowledgeable investigator (DW) perform this task.

2.6. Clinical definitions of vital signs

The following criteria were set a priori: hypotension (systolic pressure $\leqslant 80$ mmHg and/or diastolic pressure $\leqslant 50$ mmHg); hypertension (systolic pressure $\geqslant 140$ mmHg and/or diastolic pressure $\geqslant 100$ mmHg); tachycardia (HR $\geqslant 100$ bpm); bradycardia (HR $\leqslant 55$ bpm); tachypnoea (RR $\geqslant 30$ min); or pyrexia (temperature $\geqslant 39\,^{\circ}$C). Low resting heart rate (60–65 bpm), low systolic pressure (90–100 mmHg) and unrelated febrile state (37–38 °C) are common in PNG and for this reason additional restraint was incorporated in the definitions to reduce the likelihood of incorrect condition attribution. The onset of these features within one hour (within 6 h for pyrexia) of antivenom administration was recorded.

2.7. Signs of adverse reactions

The recording of one or more of the following features soon *after* start of antivenom administration was considered indicative of an adverse drug reaction: non-eruptive itching or erythematous or urticarial eruption; bronchospasm or wheeze; restlessness or agitation; headache; nausea, abdominal pain or vomiting; oedema or angioedema; laryngeal obstruction or stridor; hypotension; hypertension; tachycardia; bradycardia; tachypnoea; pyrexia; dyspnoea.

2.8. Effects of adrenaline administration

Changes in blood pressure, heart rate, respiratory rate and body temperature after antivenom administration were investigated. Measurements before antivenom and/or premedication were compared to measurements taken at 15–30 min intervals over the 6 h period following treatment and maximum 'before' and 'after' changes for each patient were recorded. The significance of the difference in median changes was compared in three groups; (a) patients with adrenaline-included premedication, (b) patients with adrenaline-excluded premedication, and (c) patients without premedication.

2.9. Statistical analysis

Reaction proportions to different pretreatments as well as associations between premedication regimes and the clinical features of reactions were compared using Fisher's exact test. Due to skewed distributions, Kruskal–Wallis tests were used to determine significance relating to changes in physiological measurements (blood pressure, heart rate, respiration rate and body temperature) and a Mann–Whitney U test was used to examine antivenom timepoint differences. All statistical analyses were conducted using SPSS® version 13.0.

3. Results

3.1. Patient demographics

Of the 136 patients who received antivenom, 75 (55.1%) were male and 61 (44.9%) female. Age was available for 111 patients. Median age of male patients was 19.0 years (range = 3.5–60 years) and 20.5 years (range = 7–80 years) for females. There were 36 paediatric cases ($\leqslant 15$ years) with a median age of 10.0 years for 25 boys and 11.0 years for 11 girls. Age data was available for 21 of the 25 patients who developed adverse reactions; median age of males was 15.0 years (range = 6–50 years), median age of females was 18.0 years (range = 9–80 years). Four patients who developed adverse reactions had their ages stated simply as 'adult'.

Table 1
Antivenom use and dosages in 136 cases of snakebite in treated in 11 rural hospitals and health centres in southern PNG

Antivenom	Quantity given	No. of patients	Percentage
CSL polyvalent	<1 vial	6	80.8%
	1 vial	99	
	2 vials	4	
	3 vials	1	
CSL polyvalent + death adder	1 vial each	1	0.8%
CSL polyvalent + blacksnake + taipan	1 vial each	1	0.8%
CSL blacksnake	1 vial	10	8.1%
	2 vials	1	
CSL death adder	1 vial	11	8.1%
CSL taipan	1 vial	1	1.4%
	2 vials	1	

3.2. Antivenoms used and dosages

Types and quantities of antivenoms used in the patient sample are presented in Table 1. Most patients (88.9%) received only one vial of antivenom. 9 patients (6.6%) received 2–3 vials and 6 patients (4.4%) received less than 1 vial. Table 2 gives information on issued antivenom supplies and documented use for the last 7 years of the review period. While 55% of supplied antivenom is unaccounted for, documented antivenom use was representative of the available antivenom inventory.

Table 2
Comparison of antivenom supplies as detailed by the PNG Department of Health and recorded usage (1998–2004) at 11 rural health centres and hospitals in southern PNG

Antivenom	Supplied	Documented use	Proportion (%)
CSL death adder	26 (9.8%)	9 (7.7%)	34.6
CSL blacksnake	20 (7.6%)	10 (8.6%)	50.0
CSL taipan	5 (1.9%)	1 (0.8%)	20.0
CSL polyvalent	213 (80.7%)	97 (82.9%)	45.5

3.3. Route of administration

Antivenom was administered by addition to intravenous fluid in 131/136 (96.3%) cases. Four patients (2.9%) received antivenom by slow intravenous injection and one patient (0.8%) received an intramuscular antivenom injection. Diluent volume was stated in only 41 cases (median = 500 ml; range = 100–1000 ml) Fluid type was stated in 43 cases: 4.3% dextrose (21), 0.9% normal saline (17), Hartmann's solution (2), Darrow's solution (2), and sterile water (1). Time taken to infuse antivenom was stated in 26 cases (median = 30 min, range = 10–924 min). Intravenous infusion times in three patients were very slow: 7 h, 9 h and 15 h 24 min, respectively. Three patients who received polyvalent antivenom by slow intravenous injection had doses administered over 20, 30 and 45 min, respectively.

3.4. Test dosing

Small intravenous test doses ranging from "a few drops" to 5 mL were given to 32 (23.5%) patients. Test doses were not given via any other route. None of these patients developed any reaction (positive test) to the test dose, but 9/25 (36%) patients who later developed adverse reactions during infusion had prior negative sensitivity tests. Only 5 of these 9 patients received specific treatment for their subsequent reactions (Table 5). The time interval between test dose administration and commencement of infusion was recorded for 19 patients (median = 5 min; range = 3–20 min).

3.5. Time between bite and antivenom administration

Paired data on bite time and subsequent antivenom administration time was available for 21 patients who experienced adverse reactions (median interval = 7 h) and for 96 patients who had no reaction (median interval = 5 h 30 min). This difference in the median time intervals was statistically significant ($p = 0.036$). Time intervals ranged from 30 to 26 h 30 min. Antivenom was administered within 4 h to 5/21 (23.8%) patients who developed adverse reactions and to 35/96 (36.4%) patients who had no reaction.

3.6. Premedication regimes, doses and routes of administration

Patient premedication regimes and reaction incidence are shown in Table 3. In total, 65/136 (47.8%) received, in some combination, adrenaline during pretreatment. The most common combination was adrenaline with promethazine (38.9%; 53/136). Adrenaline was administered subcutaneously to 63 patients at a median dose of 0.25 mg (range = 0.17–1.0 mg; 0.25 mg to 59/63). Two patients received intramuscular adrenaline pre-treatment in doses of 0.25 and 0.75 mg respectively. Promethazine was administered intravenously to 84 patients (61.8%) and intravenous hydrocortisone was given to 45 patients (33.1%); 25 patients (18.4%) received no premedication. The median promethazine dose was 25 mg (range = 6.25–100.0 mg; 25 mg to 70/84), and the median hydrocortisone dose was 100 mg (range = 75.0–500.0 mg; 100 mg to 32/45). Penicillin prophylaxis was given to 43 patients (31.6%), and 52 (38.2%) patients received 0.5 ml tetanus toxoid before antivenom administration.

3.7. Adverse antivenom reaction rates

Early adverse reactions to antivenom were reported among 25 patients (18.4%). Reactions were reported in 23 patients treated with CSL polyvalent antivenom, 1 patient treated with CSL black snake antivenom, and 1 patient treated with CSL death adder antivenom. Reaction rates for different premedication regimes are shown in Table 3. A lower incidence rate among patients given adrenaline-included premedication (7.7%) was significantly different ($p = <0.005$) to those with adrenaline-excluded premedication (28.3%) or no premedication (28.0%). Reaction rates were significantly higher ($p = <0.005$) in patients premedicated with hydrocortisone alone (40.0%) compared to those with no premedication (28.0%).

3.8. Features of reactions

Features of individual reactions are shown in Table 4. Patient 3 developed hypotension immediately after antivenom infusion but developed no other features of anaphylaxis. The incidence of skin reactions was significantly lower in patients given promethazine during premedication ($p = 0.028$). There was a significant association between adrenaline use during premedication and subsequent pyrexia ($p = 0.028$). No premedication regime was significantly associated with any other specific reaction. None of the 3 patients who developed hypertension had been administered adrenaline beforehand. One patient premedicated with promethazine rapidly developed an adverse reaction during antivenom infusion, improved after the reaction was treated, but when antivenom was recommenced 2 h later, relapsed and died after cardiac arrest (see Appendix).

3.9. Recognition and treatment of reactions

Only 11 of 25 patients received specific treatment for antivenom reactions (Table 5). Antivenom administration was briefly suspended during treatment in those cases. Adrenaline administration was subcutaneous in three, intramuscular in two, and intravenous in two others. Reactions that did not involve urticarial eruptions or impact respiratory

Table 3
Premedication regimes and subsequent adverse antivenom reaction rates among 136 patients admitted to rural health centres and hospitals in PNG

Drugs administered	No. of patients	% of patients	Reactions[a]
Adrenaline only	1	0.8	0 (0%)
Adrenaline + promethazine	53	38.9	5 (9.4%)
Adrenaline + promethazine + hydrocortisone	5	3.6	0 (0%)
Adrenaline + hydrocortisone	6	4.4	0 (0%)
Promethazine only	13	9.6	2 (15.4%)
Promethazine + hydrocortisone	13	9.6	3 (23.1%)
Hydrocortisone only	20	14.7	8 (40.0%)
None	25	18.4	7 (28.0%)

[a]Percentages shown are reaction rates for the respective premedication used.

Table 4
Features of early reactions after administration of CSL antivenoms in Papua New Guinea

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
	AP	AP	AP	AP	AP	P	P	PH	PH	PH	H	H	H	H	H	H	H	H	N	N	N	N	N	N	N
Urticaria											✓	✓	✓	✓				✓	✓						
Bronchospasm/cough/wheeze											✓	✓			✓				✓	✓					
Restlessness/agitation												✓		✓						✓					
Laryngeal obstruction/stridor						✓									✓										
Hypotension			✓			✓		✓	✓			✓							✓			✓			
Hypertension											✓				✓						✓				
Tachycardia		✓		✓	✓	✓	✓					✓		✓		✓			✓			✓	✓	✓	✓
Bradycardia						✓			✓				✓		✓										
Tachypnoea	✓			✓	✓		✓			✓		✓		✓			✓		✓			✓		✓	
Pyrexia	✓	✓			✓																✓				
Dyspnoea						✓								✓					✓	✓					
Death						✓																			

Premedication: AP = adrenaline + promethazine; P = promethazine; PH = promethazine + hydrocortisone; H = hydrocortisone; N = none.

Table 5
Treatment of identified adverse reactions to antivenom

Treatment combination	No. of cases	Percentage
Adrenaline only	1/11	9.1
Adrenaline with promethazine	1/11 (1)	9.1
Adrenaline with promethazine and hydrocortisone	5/11 (2)	45.5
Promethazine only	3/11 (1)	27.2
Promethazine with hydrocortisone	1/11 (1)	9.1

Number in brackets indicates patients who had prior negative results to antivenom test doses.

effort typically went unrecognised and were not treated. One patient with severe hypotension and bradycardia was resuscitated with 200 ml Haemaccel and slow injection of 0.5 mg i.v. adrenaline. A patient who had been premedicated with promethazine and developed severe tachycardia and tachypnoea was treated with another 25 mg i.v. promethazine.

3.10. Deaths

A total of 13 patients (9 males; 4 females; including 4 children) died despite having received antivenom (Table 6). Only one patient who died had received antivenom within 4 h of the snake bite; the minimum median time was 9 h (range = 1–25 h). The most often stated causes of death were neurotoxicity-induced airway obstruction (six cases) and respiratory failure (three cases). One death was attributed to probable anaphylaxis after antivenom administration.

3.11. Effects of adrenaline administration

There were no significant differences in maximum before and after changes to systolic blood pressure ($p = 0.558$), diastolic blood pressure ($p = 0.534$), heart rate ($p = 0.705$), respiratory rate ($p = 0.405$), or body temperature ($p = 0.49$) between the three subgroups (Table 7). One patient given 0.2 mg i.v. adrenaline with 25 mg i.v. promethazine to treat a severe reaction rapidly became tachycardic (HR = 148) but improved over 35 min, and was again premedicated with 100 mg i.v. hydrocortisone, 25 mg i.v. promethazine and 0.2 mg i.v. adrenaline before the antivenom infusion recommenced and completed without further complications. A total of 83/136 (61.0%) patients had positive 20 min whole blood clotting tests (20WBCT) and/or bleeding disorders indicative of clotting abnormalities. A negative 20WBCT was reported for 38 (27.9%) patients, while no data on coagulation status was reported for the remaining 15 patients. In total 47/65 (72.3%) patients premedicated with adrenaline had prior evidence of coagulopathy including 13/25 (52.0%) patients who developed adverse reactions. Evidence of intracranial haemorrhage (ICH) was absent from the clinical files of the patients in this study. While ICH cannot be completely excluded in two of the patients who

Table 6
Deaths from snakebite after antivenom administration in 11 hospitals and health centres in rural southern PNG

Case	Sex	Age	Features of envenomation	Antivenom	Time interval bite to AV	Premedication	Time interval AV to death
000201	M	12	Late presentation with tachycardia, lymphadenopathy, ptosis abdominal pain, diplopia, dysarthria, dysphagia, pooling oral secretions, dsypnoea. Died of airway obstruction during transport to PMGH.	1 vial polyvalent	10 h	s.c. adrenaline i.v. promethazine s.c. tetanus toxoid	2 h
004599	M	60	Patient claimed to have been bitten by a death adder. Negative 20WBCT, tachycardia and hypertension but no other details of clinical signs or cause of death.	1 vial polyvalent	1 h	s.c. adrenaline i.v. promethazine	50 min
410325	M	26	Presented with incoagulable blood, bleeding from bite site, nose and gingival sulci, ptosis, dysphagia, diplopia, dyspnoea, pooling oral secretions and peripheral muscle weakness. Died of airway obstruction at health centre.	1 vial polyvalent	>4 h	s.c. adrenaline i.v. promethazine sc tetanus toxoid i.v. Crystapen	55 min
412329	F	37	Late presentation with incoagulable blood, ptosis, diplopia, dysphagia, dysarthria, pooling oral secretions and dyspnoea who became progressively cyanotic and died of respiratory failure.	1 vial polyvalent	10.5 h	s.c. adrenaline i.v. promethazine s.c. tetanus toxoid i.v. Crystapen	4 h
025559	M	7	Late presentation in profound respiratory distress with tachypnoea, unrecordable pulse, ptosis and cyanosis. Died of respiratory failure.	1 vial death adder	21.5 h	None	75 min
058164	M	55	Late presentation with negative 20WBCT but bleeding bite site, ptosis, blurred vision, dysarthria, dysphagia, peripheral muscle weakness and dyspnoea. Poor response to first vial of antivenom but progressive improvement after second vial administered. Death due to premature removal of Guedel airway device and subsequent airway obstruction.	2 vials polyvalent	18 h	s.c. adrenaline	13 1/2 h
001671	M	5	Presented several hours after snakebite with tachycardia and incoagulable blood but no other signs. Headache, lymphadenopathy, and blurred vision apparent 1 h later and then developed ptosis, dysphagia, dyspnoea, pooling oral secretions and peripheral muscle weakness 7 h post-admission. Patient did not respond to antivenom and died of airway obstruction the next morning.	1 vial polyvalent	>9 h	None	7 h

001810	F	52	Presented within 10 min of snakebite with negative 20WBCT. Developed ptosis, blurred vision and dysarthria at 8 h post-admission and was found to have incoagulable blood with bleeding from gingival sulci. After antivenom developed pooling of oral secretions and dyspnoea. Died from airway obstruction.	3 vials polyvalent	9 h	s.c. adrenaline i.v. promethazine	14 h
055126 (sidebar)	F	A	Presented within 25 min of snakebite with negative 20WBCT and slight lymph node tenderness. Developed ptosis, blurred vision, dysphagia, dysarthria and incoagulable blood 5 1/2 h later. Patient died as a result of adverse reaction following antivenom administration.	1 vial polyvalent	7 h	iv promethazine	3 1/2 h
058125	M	10	Referred from outlying centre and presented with ptosis, blurred vision, vomiting, pooling of oral secretions, peripheral muscle weakness and dyspnoea. Respiratory effort decreased despite antivenom with cyanosis preceding death due to respiratory failure.	1 vial polyvalent	>9 h	iv hydrocortisone	2 1/4 h
057481	M	A	Presented several hours after death adder bite with negative 20WBCT, ptosis, blurred vision, lymphadenopathy, abdominal pain and dysarthria and peripheral muscle weakness. Airway obstruction led to respiratory arrest. Successfully resuscitated and given antivenom but died after second episode of airway obstruction led to further respiratory arrest.	1 vial polyvalent	>10 h	None	50 min
048365	F	A	Presented with headache, abdominal pain, vomiting, and dysphagia. After antivenom ptosis and dsypnoea developed. Patient was found asystole with fixed, dilated pupils and could not be resuscitated.	1 vial polyvalent	7 h	iv hydrocortisone	3 h
047323	M	A	Referral from outlying centre with ptosis, diplopia, dysarthria, severe arterial hypotension (200/100 mmHg), dysphagia, and peripheral muscle weakness. Patient intubated and ventilated in addition to receiving antivenom. ECG evidence of episodes of tachycardia and bradycardia with tachypnoea prior to antivenom. Patient aspirated and self-extubated 2 days post-bite followed by respiratory arrest.	1 vial polyvalent	25 h	iv promethazine i.v. hydrocortisone	24 h

Table 7
Median changes and range of variation in physiological parameters in patients pretreated with (A) adrenaline, (B) promethazine and/or hydrocortisone, or (C) no pretreatment

	A	B	C	*p*-value
Systolic BP	−10 mmHg (−70 to +30) $N = 39$	0 mmHg (−70 to +40) $N = 30$	−10 mmHg (−50 to +30) $N = 9$	0.558
Diastolic BP	−5 mmHg (−50 to +22) $N = 39$	0 mmHg (−50 to +48) $N = 30$	0 mmHg (−10 to +28) $N = 9$	0.534
Heart rate	0 bpm (−62 to +68) $N = 52$	−1 bpm (−40 to +60) $N = 42$	0 bpm (−20 to +48) $N = 15$	0.705
Respiration rate	0 per minute (−8 to +16) $N = 50$	0 per minute (−18 to +28) $N = 40$	0 per minute (−14 to +22) $N = 15$	0.405
Temperature	+0.3 °C (−0.9 to +2.5) $N = 45$	+0.15 °C (−3.1 to +2.3) $N = 38$	+0.5 °C (−1.2 to +3.0) $N = 13$	0.49

died careful analysis of the case notes did not provide sufficient information to clearly specify the cause of death. Only one of these patients had been premedicated with adrenaline.

4. Discussion

As in many tropical developing countries, rural health centres and hospitals in PNG face enormous challenges in maintaining delivery of basic medical services, and most suffer from chronic infrastructure and supply problems. Here, the treatment of snake bite envenomation involves significantly different clinical considerations compared to well-equipped modern medical facilities in Australia and other developed countries. In this study, only 7.2% of snake bite patients received antivenom, while a review of Health Department records shows that less than 50% of issued antivenom supplies were accounted for during the study period. Studies in rural PNG suggest the proportion of admitted patients with signs of systemic envenomation (neurotoxicity defined by minimum presentation with ptosis, and/or clinical bleeding indicated by a positive 20 min whole blood clotting test) may be as high as 60% (Williams, 2005), but in this study only enough antivenom to treat 14.1% of recorded snake bite patients was available.

In Australia, the use of polyvalent antivenom has declined from 41% in 1977–1978 to 31% in 1995 (Sutherland and Lovering, 1979; Sutherland, 1992; White, 1998). From 1986 to 2000 Papua New Guinea's dependence on polyvalent antivenom rose from 49% (Currie et al, 1988) to 82% while the average cost of treatment with a single vial of antivenom has increased 884% (Williams, 2005). CSL package inserts report a reaction rate of around 23% for polyvalent compared to 9% for monovalent antivenoms attributable in great part to the much higher volume of the former product (CSL Limited, 2001a, b). The observed reaction rate of 18.4% in this study of predominantly polyvalent antivenom use is consistent with these statements, but under-reporting of the true rate should not be discounted, since the study design was purely based on retrospective analysis of case records, and some patients may have experienced reactions to antivenom that went unrecorded.

This study reports a significantly lower incidence of early adverse reactions to CSL equine-derived antivenoms among patients who happened to be pretreated with low dose adrenaline. The use of subcutaneous adrenaline premedication before Australo-Papuan antivenom administration is considered risky by some toxinologists who believe it may predispose coagulopathic patients to increased bleeding and greater risk of intracranial haemorrhage (White, 1998; Currie, 2000). In Australia, bites by brown snakes (Genus: *Pseudonaja*) and to a lesser extent tiger snakes (Genus: *Notechis*) have been associated with cases of fatal intracerebral haemorrhage (Tibballs et al., 1991; Tibballs, 1994;

Sprivulis and Jelinek, 1995; Currie, 2000). Two fatal snake bites involving intracranial haemorrhages after subcutaneous adrenaline prophylaxis have been reported (Sprivulis and Jelinek, 1995) but in both cases evidence of intracranial bleeding became apparent several hours after pretreatment and adrenaline and it was speculated that this was not an aetiological factor. Studies of subcutaneous adrenaline administration have not observed hypertension (a risk factor for intracranial haemorrhage in coagulopathic patients) as an outcome of correct use (Heilborn et al, 1986; Dassanayake et al, 2002). Findings in the current study suggest that the risk of increased bleeding in coagulopathic patients after premedication with low dose subcutaneous adrenaline may be low within a New Guinean setting, but limitations in design and quality of surveillance prevent the results from being given any further weight.

While it can be argued that premedication is unnecessary in a developed country such as Australia because severe reactions to CSL antivenoms are rare and can be adequately managed by emergency physicians (White, 1998; Currie, 2000, 2003), in this Papua New Guinean study 5.1% of patients (including one who died) meet current definitions of severe anaphylaxis proposed by Brown (2004), and another 8.1% had moderate reactions which may have become more serious without intervention. Only four health facilities in this study were staffed permanently or semi-permanently by doctors during the investigation period, and only two had equipment with which to manage a respiratory emergency. There was no access to advanced life-support at the other nine health facilities. With such limited resources, taking steps to safely reduce the risk of adverse antivenom reactions through prophylaxis is appropriate. Consequently, a safe, efficacious premedication regimen for the prevention of potentially life-threatening anaphylactic reactions would be particularly relevant and important in the management of snake bite in PNG.

The variations observed in premedication regimes (Table 3) and the treatment of reactions, is a consequence of a lack of specific training and inconsistency in snake bite protocols contained in PNG's AusAID-funded paediatric and adult standard treatment books (PNG Health, 2003a, b). Even within the same health centres different premedications were used with different patients, and there was no evidence that decision-making was influenced by any concern about increased risk, such as a history of asthma or previous reaction to equine immunoglobulin. Both premedication and reaction treatment choices appeared to depend on what individual health workers had either been taught, or could discern from standard treatment books and CSL package inserts. Standard treatment books which recommend test dosing with antivenom contain no advice on what to do if the patient has a positive sensitivity test result. Hydrocortisone has previously been recommended as primary treatment for early reactions in paediatric patients, while adrenaline was recommended only for anaphylaxis (PNG Health, 2003a), and adrenaline, promethazine and hydrocortisone are recommended for the immediate management of early reactions in adult patients (PNG Health, 2003b). Early intramuscular administration of 0.1% adrenaline is essential in the emergency treatment of all anaphylactoid reactions Project Team of the Resuscitation Council (UK), 2005, and this approach should be presented in all future treatment guides. Efforts to address inconsistencies are being undertaken. The Paediatric Society of PNG recently adopted a new standard treatment protocol incorporating low dose subcutaneous adrenaline premedication (PNG Health, 2005), and it is expected that the standard treatment manual for adult patients will be adopt the same protocol in future editions. The use of (i) low dose subcutaneous adrenaline premedication and (ii) intramuscular adrenaline use in the treatment of early antivenoms reactions is currently being taught to all PNG health workers (Williams et al., 2005).

Results in this study reinforce previously published data on the unreliability of antivenom test dosing (Malasit et al., 1986; Cupo et al., 1991; Tibballs, 1994; Cupo et al., 2001; Sutherland and Tibballs, 2001). Early adverse reactions occurred in 9/32 (28.1%) patients given test doses uneventfully, accounting for 36% of all reactions. Despite clear advice against the use of test doses in CSL antivenom product information packaged with antivenom (CSL Limited, 2001a, b), standard treatment manuals include test dosing in antivenom protocols (PNG Health 2003a, b).

Although our study is limited by the nature of its retrospective design, the apparent reduction in early anaphylactoid reaction rates among patients pretreated with low dose subcutaneous adrenaline, and the lack of any detectable tachycardia, hypertension or haemorrhage in coagulopathic patients, suggests that subcutaneous adrenaline use could improve the

safety of antivenom use in rural health centres and hospitals. The inefficacy of promethazine and hydrocortisone premedication observed in this study does not support continued antihistamine and corticosteroid premedication in PNG. The role of the latter as prophylaxis for serum sickness remains untested. While we suspect that non-cutaneous reactions went largely unrecognised by health workers, and that rates reported here may be an under-estimate of the true incidence of adverse events in all patients, the results do give valuable insight into the current treatment of snake bite in rural health centres, and highlight deficiencies that should be addressed. The definitions of adverse reactions used here are more constrained than those used elsewhere (e.g. Brown, 2004) to limit over-estimation, though this may, of course, alternatively lead to under-estimation. Some single features, nominated here as adverse antivenom reactions because they manifested themselves very soon after antivenom was commenced, may also occur during the natural course of elapid envenomation. For example, patients 3 and 8 developed hypotension within 15 min of antivenom commencement, without any other signs of anaphylaxis having been reported. Although our design attributes features as being due to antivenom reactions within a narrow timeframe, the retrospective design does restrict our confidence in these attributions. Despite these limitations, this study provides valuable insight into the current clinical management of snake bite in rural health centres, and provides some indication of the incidence, and severity of adverse reactions. We plan to use the results of this study to design a comprehensive prospective trial of antivenom premedication strategies in PNG.

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Appendix. Death due to suspected anaphylaxis after antivenom administration

Time	Details
12.30pm	Elderly woman bitten on left leg by "Papuan black snake". Walks to hospital.
12.55pm	Patient admitted for observation. Blood sample in clean glass tube clots within 11 min, other than slight lymphadenopathy she is asymptomatic. Vital signs: HR 84 bpm, BP 130/80 mmHg, RR 28 breaths per min. Pressure bandage applied and observations continued.
6.30pm	Slight ptosis, blurred vision, dysarthria, dysphagia, drowsiness and dyspnoea noted. Repeat blood clotting test reveals incoagulable blood.
7.20pm	Premedication with 25 mg promethazine over 1 min.
7.25pm	Test dose of a 'few drops' of polyvalent antivenom given.
7.30pm	No reaction to test dose so remainder of polyvalent antivenom, diluted in 500 mls 4.3% dextrose put up via intravenous drip.
7.35pm	Patient develops severe respiratory distress with airway obstruction, HR 104 bpm and BP 180/80 mmHg. Antivenom stopped immediately, and reaction treated with 0.25 mg i.m. 1:1000 adrenaline, 25 mg i.v.

	promethazine and 100 mg i.v. hydrocortisone. Air viva used to assist respiration. Patient stabilized.
9.30pm	Antivenom infusion recommenced. BP drops from 180/80 mmHg to 130/80 mmHg, RR 24 breaths per minute.
10.30pm	BP 110/60, HR 108 bpm, RR 24 breaths per minute.
10.40pm	BP 70/50 mmHg, HR 68 bpm. Antivenom infusion stopped again.
10.50pm	BP and HR unrecordable. Patient arrests and resuscitation attempted.
11.00pm	Patient deceased.

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