SPECIFIC ANTIVENENE AND PREDNISONE IN VIPER-BITE POISONING: CONTROLLED TRIAL

BY

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Since the pioneer work of Calmette (1894) and Fraser (1895) it has been generally assumed that specific antivenene is the most effective treatment available for snake bite. Many reports claim support for this assumption, but to the critical mind the impressions and conclusions are vitiated by the many variables in human snake-bite poisoning. In Malaya the most common cause of snake bite is the pit viper, *Ancistrodon rhodostoma* (Boie). In 1958 a limited supply of specific *A. rhodostoma* antivenene became available for the first time in Malaya. Since the number of *A. rhodostoma* victims was much too high (Reid, Thean, and Martin, 1963) to allow each subject this specific antiserum, it was thought ethical to use the limited supply in controlled clinical trials.

A first trial comparing the effect of the specific antivenene with that of non-specific polyvalent antivenene from the Haffkine Institute, India (which had been in routine use during the preceding five years in Malaya), suggested that specific antivenene benefited systemic poisoning but did not help local poisoning. With the proviso that patients with very severe systemic poisoning would be excluded or withdrawn from the next trial, we then compared the effects of specific antivenene with those in a control group receiving no antivenene. Since steroids have also been claimed to benefit victims of snake bite we included a third group given prednisone.

Type of Patient

Snake-bite victims were admitted to the trial if (1) there was significant poisoning on arrival as revealed by local swelling totalling at least 1 cm. increase in circumference; (2) the patient was aged 10 to 69 years; (3) treatment could be started within six hours of the bite; (4) the biting snake was reliably recognized as *A. rhodostoma*. Patients with severe poisoning on arrival (shown by swelling above the knee or elbow and/or haemoptysis) were excluded.

The trial was undertaken at Sungei Patani Hospital as *A. rhodostoma* casualties are common in this district. During April, 1960, to January, 1961, we saw 212 patients with *A. rhodostoma* bites, but 107 were excluded from the trial for the following reasons: minimal or no poisoning, 79; severe poisoning on admission, 12; age under 10 or over 69, 8; and arrival more than six hours after the bite, 8.

Allocation to Treatment.—Patients were subdivided into 12 categories according to whether they were seen within two hours of the bite or over two up to six hours after the bite, were male or female, and were aged 10–19, 20–39, or 40–69. A treatment-book of 12 pages—one for each category—was kept in the out-patient department, and on each page allocation of patients was randomized to specific antivenene (A), prednisone (P), or control (C) groups. The patient's number was entered in the book, which formed the only record of the treatment given.

Withdrawals.—One patient in P group absconded and four others (one in P group, three in C group) were withdrawn because systemic poisoning became severe enough (decided by H. A. R.) to demand specific antivenene. There remain for analysis 100 patients.

Treatment

The specific *A. rhodostoma* antivenene from the Queen Saovabha Institute, Bangkok, was not refined or concentrated, and by potency tests (Purananda, 1956) 1 ml. neutralized about 0.5 mg. of venom. Ampoules were stored in refrigerators and used within a few months of issue. In the A group 50 ml. of antivenene with 1 ml. of hyaluronidase was injected into the gluteal muscle of the unbitten leg. The P and C groups received an intramuscular injection of 50 ml. of distilled water with 1 ml. of hyaluronidase. Packets with 24 tablets were numbered randomly and the numbers were entered in the treatment-book before the trial started, so that subjects in the P group received 5-mg. tablets of prednisone whereas patients in the A and C groups received indistinguishable dummy tablets. Eight tablets were given on admission, followed eight-hourly by four tablets (once), two tablets, and one tablet (each four times). Thus total dosage in the P group was 120 mg. of prednisone within three days of the bite. The appropriate packet was pinned on each patient's case-sheet. Ferrous sulphate, one tablet thrice daily, was given to all snake-bite patients. Aspirin, phenacetin, and codeine tablets could be given by the nursing staff, but were rarely needed. All patients had the ordinary ward diet. No local treatment was given apart from rest and elevation of the bitten limb: but when necrosis developed penicllin or chloramphenicol was given systemically and the eschar was removed as early as possible. Adrenaline was given for anaphylaxis and intramuscular mepyramine for later serum reactions. No other treatment was given.

Assessment of Patients

An admission form with basic data was completed for all snake-bite patients: standardized clinical assessment (by P. C. T.) was entered on a second form. Neither the observer nor the patients were aware whether antivenene or prednisone had been received. The amount of local swelling was assessed by circumference measurements to the nearest 0.5 cm. at the same marked level of both feet or hands, ankles or wrists (thinnest part), calves or forearms (fattest part), and thighs or arms (middle). Similar tension was used with the measuring-tape on both bitten and unbitten limbs. The amount of swelling was expressed in centimetres of circumference increase (total at all four measurement sites) compared with the unbitten limb or, when limbs differed in size before the bite, by comparison with the bitten limb after complete resolution of the swelling. Further observations were: extent of local swelling; pain (graded as "severe" if present at rest; "moderate" if present when moving on bed; "slight" if present only on walking); sleep and appetite (poor or

normal); presence or absence of indigestion, abdominal pain, vomiting, thirst, haemoptysis, ecchymoses, other haemorrhagic signs; blood-pressure; tourniquet test; presence and extent of blisters, limb discoloration, or necrosis; details of serum reactions; recovery time as defined by complete resolution of swelling and ability to run and jump off the bitten lower limb or (if upper limb bitten) hand-grip equal. The most sensitive indication of systemic poisoning in Malayan viper bite is clotting defect (Reid, Chan, and Thean, 1963), and in all patients the clotting-time and quality were observed daily for at least 10 days after the bite. The weight and height of each patient were measured before discharge.

Comparability of Groups

Age, sex, racial composition, and the site of the bite had a similar distribution for all groups (Table I). The average snake-length was 57.8 cm. in the A group, 60.9 cm. in P, and 59.0 cm. in C. Differences among the groups in numbers of victims killing or bringing the snake to hospital and applying a tourniquet are not significant. In no case was suction or excision employed. The site of the bite was superficially incised in two A, two P, and three C cases. A burning matchstick was applied in one A and 2 P cases. It is most unlikely that these local measures affected the issue. The average weight, height, and bite-admission intervals were similar in all three groups (Table II). Local swelling is an early and paramount feature of viper-bite-poisoning (Reid, Thean, Chan, and Baharom, 1963) and is the most valuable guide to venom dose. The average local swelling on admission (Table II) was highest in A group and lowest in C group, but the differences are not statistically significant.

TABLE I.—*Comparison of Groups*

		Specific Antivenene		Prednisone		Control	
		No.	%	No.	%	No.	%
Total No.		33	100	33	100	34	100
Age	Under 25 years	9	27	8	24	9	27
	25–39 ,,	12	36	10	30	11	32
	40+ ,,	12	36	15	46	14	41
Sex	Males	23	70	23	70	23	68
	Females	10	30	10	30	11	32
Race	Malays	17	52	19	58	23	68
	Chinese	5	15	5	15	4	12
	Indian	11	33	9	27	7	20
Site of bite	Toe	5	15	4	12	4	12
	Foot	19	58	16	49	14	41
	Leg	4	12	6	18	10	29
	Finger	3	9	5	15	5	15
	Hand	2	6	2	6	1	3
Tourniquet	Applied	25	76	30	91	28	82
	Not applied	8	24	3	9	6	18
Snake	Killed or brought in	21	64	24	73	21	62
	Escaped	12	36	9	27	13	38

TABLE II.—*Comparison of Groups*

		Specific Antivenene	Prednisone	Control
Mean weight (kg.)	Males	50·1	49·6	50·5
	Females	43·5	44·5	42·2
Mean height (cm.)	Males	158·1	158·2	160·3
	Females	150·3	151·6	149·3
Mean bite–admission interval (hours)		1·6	1·8	1·5
Local swelling on admission (cm.)	Mean	3·2	2·8	2·4
	Range	1·0–7·5	1·0–7·5	1·0–6·0

Results of Treatment

Local Poisoning.—The post-admission increase of local swelling in C group (4.0 cm.; range 0.5–14) was somewhat higher than in A (3.2 cm.; range 0–12.5) and P (3.2 cm.; range 0–9.5) groups, but in general the amount of swelling increase was related to the bite-admission interval, being greatest in those patients coming to hospital soonest (Table III). Patients receiving antivenene within one hour of the bite had less average swelling increase (2.7 cm.) than those receiving prednisone (5 cm.) or control (5.5 cm.) treatment, but the differences are not significant ($0.6>P>0.5$ and $0.5>P>0.4$). The average time taken for swelling to resolve, recovery to occur, and pain to disappear showed no striking differences between the groups (Table IV). When pain is divided into grades the incidence is similar in all groups, as are the occurrence and healing-times of necrosis. Ten of the 14 patients with necrosis were bitten on a toe or finger, where, owing to high local concentration of venom, the risk of necrosis is known to be higher than in bites elsewhere (Reid, Thean, and Martin, 1963). Incorporation of necrosis-healing times with "recovery times" yields similar figures for each group. Analysis of all these features according to bite–admission interval, as in Table III, showed no statistically significant differences between the groups.

Systemic Poisoning.—This was graded as severe when a haemorrhagic state was clinically evident, moderate if blood would not clot but no haemorrhagic symptoms developed, and slight if blood-clotting was poor in quality (Reid, Chan, and Thean, 1963). A highly significant number of patients developed systemic poisoning in the P and C groups. Adding the four cases withdrawn, 18 (53%) in P group (4 severe, 10 moderate, and 4 slight) and 16 (43%) in C group (5 severe, 10 moderate, and 1 slight) developed systemic poisoning, compared with only 3 (8%) in A group. In the latter, moderate systemic poisoning developed after one to three days with normal blood-clotting. Statistically the differences between the percentages (P–A 45 ± 10.7 and C–A 35 ± 10.2) are highly significant. The mean duration of the clotting defect (excluding the four withdrawn cases in which specific antivenene had to be given) was similar in both the P (13.8 days) and the C (14.7 days) groups.

Other Features.—Local blisters and limb discoloration, fever, poor sleep and appetite, indigestion, abdominal pain, vomiting, and thirst were uncommon and the incidence of these features was similar in all three groups. Antivenene reactions developed in 10 (30%) of the antivenene group. Moderate anaphylaxis occurred in two cases; later serum reactions were severe in three cases, moderate in four, and slight in one.

TABLE III.—*Swelling by Bite–Admission Interval*

Bite–Admission Interval (Hours)	Specific Antivenene		Prednisone		Control	
	No.	Swelling (cm.)	No.	Swelling (cm.)	No.	Swelling (cm.)
1 or less	7	2·7	5	5·0	4	5·5
Over 1 and under 2	13	3·2	15	3·7	15	4·2
,, 2 ,, ,, 3	8	4·5	9	1·9	11	3·5
,, 3 ,, ,, 6	5	2·0	4	1·8	4	3·1
Total	33	3·2	33	3·2	34	4·0

TABLE IV.—*Post-treatment*

		Specific Antivenene	Prednisone	Control
Average No. of days to swelling resolution		13·6	15·7	13·7
Average No. of days to recovery *		14·5	19·2	14·3
,, ,, ,, ,, ,, pain resolution (all grades)		12·2	13·2	11·0
Pain—No. with	None	1	1	0
	Slight only	4	6	4
	Moderate only	13	9	16
	Severe	15	17	14
Necrosis	No of patients	2	4	3
	Mean healing-time (days)	42	38	55

* This excludes necrosis healing-time.

Discussion

Opportunities for research into *A. rhodostoma* bites are probably unique in the large number of human victims available for study and in the high degree of reliable identification of snake species. The main reason for both these features is that, unlike most other snakes, *A. rhodostoma* does not move away even when disturbed to the extent of biting humans. It is noteworthy that only one-half of the patients available were acceptable into the trial, the chief reason for rejection being minimal or no poisoning.

The three groups in the trial were similar in the variables measured before treatment, the small differences observed being within the limits of random fluctuation. Serum reactions could indicate to the observer that specific treatment had been given, but since they were mostly delayed until several days later, when the important assessment observations had already been made, we think observer-bias through this factor is unlikely.

The effectiveness of specific antivenene in combating systemic *A. rhodostoma* poisoning—despite its feeble potency as judged by customary laboratory tests—is amply confirmed. A prolonged coagulation defect is the outstanding characteristic of systemic *A. rhodostoma* poisoning (Reid, Chan, and Thean, 1963) and the difference in incidence and severity of this defect between the group treated by specific antivenene (8% ; no severe cases) and those receiving prednisone (53% ; 4 severe cases) or control treatment (43% ; 5 severe cases) is statistically very significant. The benefit to individual patients has already been reported in more detailed studies (Reid, Chan, and Thean, 1963). Furthermore, the latter studies showed that specific antivenene was highly effective even though not given until several *days* after the bite. In victims with very severe systemic poisoning, particularly in those with shock (such patients were excluded from this trial), the clinical improvement following specific antivenene can justifiably be described as dramatic.

In contrast, the clinical features of local poisoning showed no significant difference between the three groups. It is therefore likely that specific antivenene, though beneficial in systemic poisoning, is largely ineffective in combating local *A. rhodostoma* poisoning. Experience with higher and lower antivenene dosage and with the intravenous route does not change this conclusion. Though sometimes necessary, intravenous antivenene injection greatly increases the risk of serum reactions, which is already high, being 30% with the trial antivenene using the intramuscular route. Injection of specific antivenene locally into the area of the bite might be expected to combat local poisoning, but a further controlled trial would be needed to evaluate the effectiveness of such a procedure. We consider the risk of introducing bacterial infection (Reid, Thean, Chan, and Baharom, 1963) is a major drawback to local injection.

Almost inevitably, steroids have been vaunted for viper-bite poisoning (Hoback and Green, 1953 ; Gowdy, 1954). But the evidence is not convincing, and neither Schöttler (1954) nor Russell and Emery (1961) could confirm any benefit experimentally. In this trial we found prednisone of no help either in local or in systemic poisoning.

Summary

In Northern Malaya conditions are exceptionally favourable for studying human victims of the pit viper *Ancistrodon rhodostoma* (Boie). The results of a double-blind controlled therapeutic trial in moderate poisoning following bites of this snake are described.

The purpose of the trial was to see if specific antivenene given within six hours of the bite and prednisone started within six hours of the bite produced better results than control treatment.

The trial was carried out at Sungei Patani Hospital: 105 patients aged 10 to 69 years inclusive were admitted to the trial, but subsequently five subjects were withdrawn. Patients were allocated at random to one of three treatment schedules: (1) specific antivenene 50 ml. with 1 ml. of hyaluronidase by intramuscular injections, dummy tablets ; (2) distilled water 50 ml. with 1 ml. of hyaluronidase by intramuscular injection, prednisone tablets totalling 120 mg. within three days of the bite ; and (3) distilled water 50 ml. with 1 ml. of hyaluronidase by intramuscular injection, dummy tablets.

Statistical analysis shows that the difference between incidence and severity of systemic poisoning in the antivenene group and in the groups receiving prednisone or control treatment was highly significant. In contrast, there was no statistically significant difference between the clinical features of local poisoning in these three groups.

Thus specific antivenene is very effective in combating systemic poisoning following bites of the pit viper *A. rhodostoma* but does not appear to help local poisoning. Prednisone seems to benefit neither systemic nor local poisoning.

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