PAPERS AND SHORT REPORTS

Prediction, prevention, and mechanism of early (anaphylactic) antivenom reactions in victims of snake bites

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Abstract

Victims of snake bites are often subjected to cutaneous or conjunctival hypersensitivity testing before being given antivenom. None of 12 early (anaphylactic) reactions was predicted by these tests in 25 Nigerian and Thai patients. The incidence and severity of early reactions was the same whether antivenom was given by intravenous injection over 10 minutes or diluted and given as an intravenous infusion over 30 minutes. Although antivenom activated complement in vitro, there was no evidence of complement activation or formation of immune complexes in patients bitten by snakes who were treated with antivenom, whether or not they developed early reactions. Higher doses of antivenom might induce the complement activation and formation of immune complexes (aggregates) that have been observed during the clinically more severe reactions associated with homologous immunoglobulin treatment.

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Introduction

Antivenom, the serum of animals immunised with venom, is the only specific treatment for poisoning with snake venom. It is most effective by intravenous injection,[1,2] but some patients quickly develop cutaneous or systemic anaphylaxis when it is given in this way. The incidence and severity of these early reactions is proportional to the dose of antivenom and the speed with which it enters the blood stream.[3] The reported incidence of early reactions after intravenous antivenom ranges from 3% to 54%[4-8]; this depends partly on the quality of clinical observation during the critical one to two hours after treatment.

In most cases symptoms are mild: urticaria, nausea, vomiting, diarrhoea, headache, and fever; but in up to 40% of cases severe systemic anaphylaxis develops with bronchospasm, hypotension, or angioneurotic oedema. Surprisingly few deaths have been reported,[5,8-10] but some anaphylactic deaths may have been wrongly attributed to envenoming. Mortality of anaphylaxis from other antisera was reported as 0·1%.[11] In England the death of an asthmatic boy from anaphylaxis induced by antivenom in 1957 led to the rejection of antivenom treatment on the grounds that the bite was less dangerous than the treatment.[10,12,13]

Skin or conjunctival sensitivity tests have proved unreliable in predicting early reactions to antivenom[4,14,15] and reactions to other equine antisera,[16,17] but advocates are still found.[14,18-20] There have been no published reports of the value of sensitivity tests for antivenom treatment based on prospective studies. Early reactions were previously regarded as type I immediate hypersensitivity reactions to equine serum proteins, but their prevalence in populations never exposed to horses[7] and the absence of specific cutaneous hypersensitivity in most reactive patients have prompted a search for other mechanisms. Sutherland found that eight out of nine commercial antivenoms were anticomplementary in vitro.[21] These results led him and others to recommend slow intravenous infusion of diluted antivenom to reduce complement activation.[8,15] This method, however, requires more equipment and supervision than the intravenous ("push") injection that is widely used in tropical countries, and its benefits have not been proved. We studied some of these problems of antivenom treatment in patients bitten by snakes.

Patients and methods

In Bambur General Hospital and Ahmadu Bello University and Wusasa Hospitals, Zaria, northern Nigeria, we studied 15 patients with systemic envenoming by the saw-scaled or carpet viper (*Echis carinatus*). In Queen Saovabha Memorial Institute (Thai Red Cross Society), Bangkok and Trang Provincial Hospital and Pra Pokklao Provincial Hospital, Chantaburi, Thailand, we studied 19 patients with local or systemic envenoming by green pit vipers (*Trimeresurus albolabris* and *T macrops*), two patients with local envenoming by the monocellate Thai cobra (*Naja kaouthia*), and 59 patients with systemic envenoming by the Malayan pit viper (*Calloselasma rhodostoma*). Patients gave written informed consent to take part in the study, which had been passed by local ethical committees.

SENSITIVITY TESTS

In Nigeria liquid antivenoms (*Bitis-Echis-Naja* polyspecific antivenom, Behringwerke, West Germany, and *Echis* monospecific antivenom, Institut Pasteur, Paris) were diluted 1 in 10 in isotonic saline: 0·02 ml was given intradermally into the left forearm of 15 patients,[14] and one drop was instilled into the left conjunctival sac. Plain isotonic saline (0·02 ml) was injected intradermally into the right arm and one drop of saline instilled into the right conjunctival sac as controls.

In Thailand one ampoule of lyophilised antivenom (freeze dried green pit viper monospecific and Malayan pit viper monospecific antivenoms, Thai Red Cross, Thailand) was reconstituted with 10 ml of sterile water and 0·2 ml of this solution injected subcutaneously into the left forearm of 20 patients.[22] Plain isotonic saline (0·2 ml) was injected subcutaneously into the opposite arm as a control.

The patients were observed closely for 30 minutes after injection and instillation. The diameter of swelling and erythema on test and control forearms was then measured. Redness and itching were recorded in the patients in whom conjunctival tests had been performed. In every case the antivenom used for sensitivity testing was the same as that given subsequently for treatment of envenoming. All antivenoms were of equine origin.

COMPARISON OF INTRAVENOUS INJECTION AND INFUSION OF ANTIVENOM

Sixty six Thai patients with local or systemic envenoming by green pit vipers, Malayan pit vipers, or cobras were randomly allocated into two groups for treatment with either infusion or injection. Nineteen patients with bites from green pit vipers were given one or five vials of Thai Red Cross freeze dried monospecific antivenom and 48 patients with bites from Malayan pit vipers were given five vials of Thai Red Cross freeze dried (equine), Thai Government Pharmaceutical Organisation freeze dried (equine), or Twyford Pharmaceuticals liquid monospecific (caprine) antivenoms. Freeze dried antivenoms were dissolved in water (10 ml/ampoule) and were either injected intravenously, without further dilution, over 10 minutes exactly or added to 200 ml of isotonic saline and infused intravenously over 30 minutes.

Patients were observed closely for at least six hours after antivenom treatment. The timing and severity of early reactions were recorded. At the first sign of a reaction 0·5 ml of 0·1% adrenaline was injected subcutaneously followed by 10 mg of chlorpheniramine maleate by slow intravenous injection.

IMMUNOLOGICAL STUDIES

Blood samples were taken from 28 Thai patients with local or systemic envenoming from green pit vipers, Malayan pit vipers, or cobras before sensitivity tests were performed; immediately before the start of antivenom treatment; five, 15, 30, and 120 minutes later; and at the first sign of an early reaction. Plasma containing 0·1 mmol/l (3 mg/100 ml) edetic acid and serum were collected and stored at −70°C until used. Serum samples were assayed for immune complexes by three methods: iodine-125 protein A assay,[23] C1q binding,[24] and solid phase conglutinin[25] with ^{125}I protein A instead of ^{125}I anti-IgG to detect bound immune complexes. Protein A, purchased from the Public Health Laboratory Service, Porton Down, Wiltshire, was labelled with ^{125}I by the iodogen method (Pierce Chemical Company).[26] For each analysis results that were more than two standard deviations away from values from a group of 25 healthy controls were regarded as positive.

Complement components and breakdown products were measured in samples of plasma containing 0·1 mmol/l edetic acid. C3 and C4 were measured by radial immunodiffusion with monospecific antisera. C3 breakdown products were detected with two dimensional immunoelectrophoresis with specific antisera against C3 and C3b.[27] Breakdown products were expressed as a percentage of the total amount of C3.

TABLE I—*Results of sensitivity tests in 25 patients bitten by snakes*

No of patients	Country	Biting species of snake	Severity of envenoming (No of patients)	Administration route of antivenom	Dose of antivenom (ampoules)	Positive results: No of patients	Positive results: No of reactions to treatment	Negative results: No of patients	Negative results: No of reactions to treatment	Negative results: No of severe reactions
15	Nigeria	*Echis carinatus*	Systemic	Corneal	2 P or 6 B	1	0	14	3	1
				Intradermally 0·02 ml (1 in 10 dilution)		0	0	15	3	1
20	Thailand	*Trimeresurus albolabris*	Local (12)	Subcutaneously 0·2 ml (neat)	1 TRC	1	0	19	9	1
		T macrops	Systemic (3)		5 TRC					
		Calloselasma rhodostoma	Systemic (4)							
		Naja kaouthia	Local (1)							

P=Institut Pasteur *Echis carinatus* monospecific antivenom; B=Behringwerke *Bitis-Echis-Naja* polyspecific antivenom; TRC=Thai Red Cross monospecific antivenom.

C3d was detected by double decker immunoelectrophoresis with a monospecific antiserum against C3d (Dakopatts, Denmark). Results were expressed as a percentage of C3d in an aged plasma pool.[28]

ASSESSMENT OF IN VITRO COMPLEMENT ACTIVATION BY ANTIVENOM

Lyophilised green pit viper antivenom (Thai Red Cross) was reconstituted with sterile water. Increasing amounts (2-25 μl) were added to 25 μl of normal human serum and incubated at 37°C for 30 minutes. The mixture was assayed for complement breakdown products by crossed immunoelectrophoresis. In a second experiment reconstituted antivenom was spun at 10 000 *g* for 30 minutes to remove aggregates. Controls consisted of additions of edetic acid at a final concentration of 10 mmol/l (292 mg/100 ml) (to inhibit the classical and alternative pathways of complement activation) and ethyleneglycol tetra-acetic acid and magnesium chloride at final concentrations of 10 and 7 mmol/l (380 and 142 mg/100 ml), respectively (to inhibit the classical pathway of complement activation); normal serum alone; and reconstituted antivenom alone.

STATISTICAL METHODS

Fisher's exact test, χ^2 test, and two tailed *t* test were used for statistical analyses.

Results

SENSITIVITY TESTS

Table I gives the results of sensitivity tests in 25 patients bitten by snakes. None of the 12 early reactions (two of them severe) in the 25 patients was predicted by a positive result from the skin or conjunctival test. The two patients in whom positive results were yielded from the tests did not have reactions. Five patients developed late serum sickness type reactions five to

TABLE II—*Comparison of intravenous injection and infusion of antivenom in 66 Thai patients bitten by snakes*

Biting species of snake	Severity of envenoming (No of patients)	Antivenom: Manufacturer	Antivenom: Specificity	Antivenom: Dose (ampoules)	Infusion: No of patients	Infusion: No of reactions	Infusion: No of severe reactions	Injection: No of patients	Injection: No of reactions	Injection: No of severe reactions
Trimeresurus albolabris	Local (12)	TRC	Green pit viper	1	8	3	0	7	2	6
T macrops	Systemic (3)									
T albolabris	Systemic	TRC	Green pit viper	5	2	1	0	3	2	1
Calloselasma rhodostoma	Systemic	TRC, TGPO, Twyford	Malayan pit viper	5	23	14	5	23	10	4
Total					33	18*	5†	33	14*	6†

TRC=Queen Saovabha Memorial Institute (Thai Red Cross Society), Bangkok; TGPO=Thai Government Pharmaceutical Organisation, Bangkok; Twyford=Twyford Pharmaceuticals GmbH, Ludwigshafen.
*$\chi^2=0{\cdot}97$, $p>0{\cdot}3$. †$\chi^2=0{\cdot}97$, $p>0{\cdot}3$.

TABLE III—*Details of 28 Thai patients bitten by snakes included in immunological studies of early reactions to antivenom*

Biting species of snake	Severity of envenoming (No of patients)	Thai Red Cross antivenom: Specificity	Thai Red Cross antivenom: Dose (ampoules)	Thai Red Cross antivenom: Method of administration	Total No of patients	Negative results from skin tests: No of patients	Negative results from skin tests: No of reactions (severe)	Positive results from skin tests: No of patients	Positive results from skin tests: No of reactions	Skin test not done: No of patients	Skin test not done: No of reactions (severe)
Trimeresurus albolabris	Local (12)	Green pit viper	1	Infusion	8	8	3	0	0	—	3 (0)
T macrops	Systemic (3)			Injection	7	6	2 (1)	1	0	—	—
Calloselasma rhodostoma	Systemic	Malayan pit viper	5	Infusion	11	4	2 (2)	0	0	7	3 (0)
Naja kaouthia	Local	Cobra	5	Infusion	2	1	1 (0)	—	—	1	0
Total					28	19	8 (3)	1	0	8	6 (0)

TABLE IV—*Immunological results in 26 healthy Thai controls and 28 patients bitten by snakes*

Assay	Controls: No of samples	Controls: Mean (2 SD) %*	Snake bitten patients: No of samples	Snake bitten patients: Mean (2 SD) %*	
Complement components:					
C3	25	124·1 (60·4)	103	97·2 (50)	
C4	26	112·4 (93·6)	103	91·3 (80)	
C3b	26	0	103	0	
C3d	26	0	103	0	
		Mean (2 SD) % binding		No of positive results (mean (2 SD))	No of negative results
Immune complex assays:					
Protein A binding	19	2·25 (2·06)	229	10 (5·8 (2·0))	219
C1q binding	20	1·56 (1·34)	237	34 (6·8 (5·0))	203
Conglutinin	20	2·76 (1·49)	104	17 (13·7 (19·8))	87

* % Of a pool of 120 plasma samples from healthy Thai subjects.

17 days after receiving total doses of 10-200 ml of antivenom. In none of these patients were positive results yielded from skin tests. Follow up was not adequate for an assessment of the incidence of late reactions.

COMPARISON OF INTRAVENOUS INJECTION AND INFUSION OF ANTIVENOM

There was no significant difference in the incidence or severity of early reactions between the group of 33 patients given diluted antivenom by infusion and the other group of 33 given undiluted antivenom by intravenous injection (table II).

IMMUNOLOGICAL STUDIES

Table III gives the details of the 28 Thai patients included in the immunological studies of early reactions to antivenom. Eleven of these 28 patients had early reactions. Plasma samples obtained before the skin test was performed and five and 30 minutes after the start of intravenous antivenom treatment were assayed blind for complement components and breakdown products. All the results were within the range (mean (SD)) of a group of healthy subjects (see table IV). All samples from the 11 patients who reacted to antivenom were then assayed, including those taken at the first sign of the reaction. Results from these assays were also within the normal range. Pooled results from all 103 samples that were analysed, for both C3 and C4, did not differ significantly from the 26 control samples (table IV). C3b and C3d were not detected in any of the samples from patients or controls.

Most of the serum samples were assayed blind for immune complexes with protein A and C1q binding assays. Samples from the 11 reactive Thai patients were also tested by the conglutinin binding assay. Immune complexes were detected by one or more assays in six patients, but in all cases they were present in samples taken before skin tests were performed and after treatment. There was no consistent change in binding activity after antivenom treatment and no association between the presence of complexes and the development of an early reaction.

ASSESSMENT OF IN VITRO COMPLEMENT ACTIVATION BY ANTIVENOM

In vitro testing showed dose dependent antivenom activation of complement by both classical and alternative pathways. Removal of aggregates by centrifugation reduced this activation. The smallest ratio of the amount of antivenom to normal serum giving significant C3 conversion was 1:6·3. This would be equivalent to giving 400 ml of antivenom to a person with a blood volume of 5 l.

Discussion

Many authorities on snake bites have recommended the use of sensitivity testing but at the same time provided evidence of its unreliability[4 14 18-20 29 30] and even potential lethality.[20] Others have considered this test to be useless.[3 8 15 21] Neither opinion has been backed up by prospective data. Results of our sensitivity tests in 25 Nigerian and Thai patients prove that these conventional tests have no predictive value for the occurrence of early reactions, even severe system anaphylaxis. It is not justifiable to delay antivenom treatment for 20 or 30 minutes to read the results of sensitivity tests. As early reactions are common, unpredictable, and occasionally life threatening all patients treated with antivenom must be regarded as potentially reactive. We were unable to study late serum sickness type reactions, but published reports provide no convincing evidence that they are predicted by the results of sensitivity tests.

Most authorities recommend that antivenom should be diluted in 200-500 ml[20 22] or more of isotonic fluid and given by slow intravenous infusion. The rate of administration can be more easily controlled by this method, but it has serious disadvantages in the rural tropics where most cases of snake bite occur. Intravenous fluids and administration sets are expensive, they take longer to set up, and the fluid may run in precipitously unless supervised. In this study the slow infusion of diluted antivenom given to 33 patients did not decrease the incidence or severity of early reactions. An advantage of the intravenous "push" injection given over 10 minutes is that the person giving the injection must remain with the patient during the period when most severe anaphylactic reactions develop. By increasing the dilution of antivenom and prolonging its infusion we might have produced a different result, but the danger of overloading with fluid, especially in children, and the urgent need to neutralise circulating venom precludes these methods.

Reactions to homologous immunoglobulin resemble reactions to antivenom in that they are not predicted by the results of skin tests.[31] Severe vasomotor symptoms are commoner after homologous serum has been given,[32 33] but urticaria, the commonest manifestation of antivenom reactions, is rarely mentioned in accounts of these reactions. The differences may be explained by the fact that at least 10 times more human than equine protein is administered (200 mg human protein/kg body weight, or 10 g of human protein for a patient weighing 50 kg compared with 1-5 g of equine protein for the same patient).

There is convincing evidence that early reactions to homologous serum and late serum sickness type reactions to antivenom are related to complement activation by immune complexes (aggregates).[32 34] Complement activation and immune complexes were detected after infusion of human immunoglobulin, even in those patients who remained asymptomatic. In accord with Sutherland,[21] we found that the Thai Red Cross antivenom activated complement in vitro. Fairly large amounts of antivenom were required, however, and in vivo there was no evidence of complement activation or the appearance of immune complexes after antivenom treatment, even in the 11 patients who had overt reactions (three of them had severe generalised anaphylaxis). Complement activation was unlikely to have been missed as we used sensitive assays and took frequent samples.

Hypogammaglobulinaemic patients appear more susceptible to homologous serum reactions than others, and Soothill suggested that the patients' ability to filter out aggregates may determine whether they develop a reaction.[31] If the removal of circulating IgG aggregates by the reticuloendothelial system was more efficient in our healthy patients bitten by snakes given equine serum than in immunosuppressed and hypogammaglobulinaemic patients given homologous serum the differences in severity of reactions and detection of immune complexes would be partly explained.

Several snake venoms are known to activate complement by the classical or alternative pathway,[34] and reduced concentrations of complement components and complement breakdown products have been detected in serum samples from envenomed patients.[35] These changes were not detected before antivenom treatment in the patients studied in Thailand, probably because many of them were mildly envenomed.

Fatal anaphylaxis is the main hazard of antivenom treatment. Rare disasters have led to the wholesale rejection of antivenom treatment.[10 12 13] Further studies are needed to discover the mechanism of early reactions. The idea of complement activation, already shown in patients given large doses of homologous serum, is attractive but has not yet been shown convincingly in victims of snake bites.

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