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THE EFFICACY OF HYPERIMMUNE SERUM IN THE TREATMENT OF SWEATING SICKNESS

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ABSTRACT

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Natural and experimental cases of sweating sickness were treated using a hyperimmune serum as specific treatment and hyperimmune serum combined with symptomatic and supportive treatment based on the clinico-pathological changes observed in cases of sweating sickness. The treatment regimens were found to be highly effective in pigs and sheep as well as in calves, although recovery in the latter species was slower.

INTRODUCTION

The treatment of sweating sickness has always been based on symptomatic and supportive measures, with the emphasis on good nursing, but it is generally regarded as unsatisfactory (Lawrence, 1946; Neitz, 1959; Van Amstel, 1984).

Until recently, the procedures of treatment were empirical and included dosing the animals with liver meal (Neitz, 1959) and the intravenous injection of formalin, measures which were reported to result in a significant improvement (Bezuidenhout & Oberem, 1984). Aspirin, aureomycin, ferrous sulphate, penicillin, phenanthridinium, promethazine hydrochloride, quinine, sulphadimidine sodium and trypan blue reportedly had some beneficial effect (Neitz, 1959).

Current treatment involves the replenishment of fluids and the administration of antibiotics to prevent and treat secondary bacterial infection. Anti-inflammatory drugs are also frequently used. Care must be taken not to exacerbate nephrosis and hepatitis, commonly seen in cases of sweating sickness (Van Amstel, 1984).

The beneficial effect of any treatment must be carefully evaluated, as spontaneous recovery does occur, particularly if the causative ticks are removed at an early stage of the disease. Nevertheless, the mortality in cattle suffering from sweating sickness can be higher than 75 % (Neitz, 1959), while Clark (1933) found it to be as high as 77 %. Conversely Bisschop (cited by Neitz, 1959) estimated the mortality to be as low as 29 %.

In cases which recovered, Neitz (1959) reported the course of the disease to be 4–20 days with a mean of 6 days. The course of the disease in sheep is 4–9 days with a mean of 6 days. Mortality in sheep varies greatly, but it can be as high as 95 % if the sheep are fully susceptible. In pigs Neitz (1959) documented a 55 % mortality and a course of 4–24 days with a mean of 8 days.

In recent years the incidence of the disease appeared to have declined (South African Department of Agriculture, 1975–1982). Reports received from the field during 1983 and 1984 of 5 %–8 % morbidity on farms in the northern Transvaal indicated, however, that the disease is still a problem in certain areas. The fact that no help, other than advice and symptomatic and supportive treatment based mainly on older literature and experience, was available to the farmers stimulated a search for a specific treatment.

Similarities between this disease and the paralysis caused by *Ixodes holocyclus* Neuman, as well as the effective use of an antiserum against *I. holocyclus* paralysis by the Australian Commonwealth Serum Laboratories, Melbourne (Oxer & Ricardo, 1942), determined the direction taken in this project.

MATERIALS AND METHODS

Preparation of hyperimmune serum

Sheep and cattle selected for the production of hyperimmune serum were repeatedly (2–5 times at 6-week intervals) infested with 30–50 male and female *H. truncatum* ticks kept at the Veterinary Research Institute, Onderstepoort and known to cause sweating sickness, as listed in Table 1 (Bezuidenhout & Malherbe), 1981).

Five days after the initial challenge with ticks the animals developed sweating sickness, diagnosed on history and symptomatology. The ticks of the later infestations engorged, but the animals showed no signs of sweating sickness other than, in some cases, a temperature reaction 3 days after the ticks attached. The animals were finally challenged *c.* 1 week before they were to be bled as serum donors. Details of the animals and tick strains used as well as the number of times each prospective donor was challenged are given in Table 2.

The animals were usually bled 7 days after the last batch of ticks had engorged and dropped. In one case, serum that was used to treat sheep was taken from a donor sheep, Sheep 6522, which had been challenged for the second time almost 6 weeks prior to its being bled as a donor. About 500 mℓ of blood was taken from each sheep and 2 ℓ from each bovine. The blood was collected, with sterile precautions, allowed to clot at room temperature for *c.* 20 h, after which the serum was collected. Serum not immediately used was stored at −18 °C.

In the treatment of 3 field cases, fresh whole blood from donor animals collected in acid citrate dextrose was used.

Treatment of animals with sweating sickness

Not all the animals obtained from areas where *H. truncatum* is absent are susceptible to sweating sickness (Bezuidenhout & Oberem, 1984). Despite ticks of a virulent strain being fed on these animals for the first time, they do not always develop sweating sickness. For this reason, only animals which developed clear symptoms of sweating sickness were taken into account and used.

Control cases. Sixty-three (1 pig, 2 cattle and 60 sheep) cases of sweating sickness have been elicited over a 3-year period. Several cases were produced experimentally in a way similar to that used to produce the hyperimmune serum. The majority of cases were produced during routine feeding of the sweating sickness causing strains of *H. truncatum*, while some cases consisted of sheep used in other sweating sickness trials. Most were not treated in any way while 4 were treated with long

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TABLE 1 List of strains of *H. truncatum* and their disease-causing capacity kept at this laboratory

Strain	Ability to cause sweating sickness
Uitenhage (Uit.)	Positive
South West Africa (SWA)	Positive
Zululand (Zulu)	Positive
SWA × Uitenhage (SWA × Uit.)	Positive
Kaalplaas	Negative
Mkuzi	Negative
Warrenton	Negative

TABLE 2 List of donor animals including the number of times challenged and the strain of tick used

Animal No.	Tick strain	Number of times challenged	Reaction
545 (B)	SWA × Uit.	1	None
	SWA	2	None
8094 (B)	Uit.	1	SS
	Uit.	2	None
	SWA × Uit.	3	None
	SWA	4	None
6238	SWA × Uit.	1	SS
	SWA	2	None
	Uit.	3	None
6204	SWA × Uit.	1	SS
	SWA	2	None
	Uit.	3	None
5683	SWA × Uit.	1	SS
	SWA × Uit.	2	None
	SWA	3	None
	SWA × Uit.	4	None
	SWA × Uit.	5	None
6522	Uit.	1	None
	Uit.	2	None
	Uit.	3	None
5689	Kaalplaas	1	None
	SWA	2	SS
	Uit.	3	None
5654	SWA	1	SS
	SWA	2	None

(B) = Bovines

acting penicillin*, and the ticks on 2 of them were killed by the application of an acaricide** at the recommended dosages.

Experimental cases. The disease was elicited in sheep, pigs and calves by feeding on them between 30 and 50 male and female ticks of strains causing sweating sickness. The animals were monitored daily for the typical symptoms of sweating sickness, which include a variable temperature reaction, generalized hyperaemia of the skin, congestion of the mucous membranes, serous and later mucopurulent occulo-nasal discharge, listlessness and anorexia (Neitz, 1959). Once the animals showed unmistakably the above symptoms, they were treated with various dosages of hyperimmune serum given per drip intravenously (Tables 4, 5 & 6). The appetite, habitus, rectal temperature and symptomatology of the animals were monitored and recorded daily. The ticks were not removed nor was any additional treatment, either symptomatic or supportive, administered.

In all cases, the time taken to recover was recorded. This period was regarded as the time from when the animal was first seen visibly to be suffering from sweating sickness to the time when its appetite, habitus and mucous membranes returned to normal. If the body temperature of the animal had been elevated, which was not a constant-finding, its return to normality was also regarded as a sign of recovery.

TABLE 3 The outcome of sweating sickness in untreated control animals

Animal No.	Tick strain	Treatment (if any)	Results
6945	Uit.	None	Died
6583	Uit.	None	Died
6451	Uit.	None	Died
5836	Uit.	None	Died
5825	Uit.	None	Died
5556	Uit.	None	Died
3920	Uit.	None	Died
3873	Uit.	None	Died
6601	Uit.	Antibiotic	Recovered on Day 4
6600	Uit.	None	Recovered on Day 4
6595	Uit.	Antibiotic	Recovered on Day 5
5824	Uit.	Antibiotic	Died
5583	Uit.	None	Recovered on Day 3
5278	Uit.	Acaricide	Recovered on Day 3
5263	Uit.	Acaricide	Recovered on Day 4
6590	Uit.	None	Recovered on Day 5
5842	Uit.	None	Recovered on Day 3
5801	Uit.	None	Recovered on Day 6
5262	Uit.	None	Died
4286	Uit.	None	Recovered on Day 5
3977	Uit.	None	Recovered on Day 4
3973	Uit.	None	Recovered on Day 4
5555	Uit.	None	Died
3570	Uit.	None	Died
3326	Uit.	None	Died
3317	Uit.	None	Died
2439	Uit.	None	Died
2412	Uit.	None	Recovered on Day 5
2407	Uit.	None	Recovered on Day 6
2406	Uit.	None	Died
2403	Uit.	None	Died
2396	Uit.	None	Recovered on Day 2
1712	Uit.	None	Died
1700	Uit.	None	Died
1694	Uit.	None	Died
1650	Uit.	None	Recovered on Day 5
1072	Uit.	None	Died
5981	SWA	None	Recovered on Day 7
6947	SWA	None	Died
6574	SWA	None	Recovered on Day 5
6480	SWA	None	Died
6463	SWA	None	Recovered on Day 10
6449	SWA	None	Died
5689	SWA	None	Recovered on Day 4
5554	SWA	None	Recovered on Day 3
5282	SWA	None	Died
5256	SWA	None	Died
5282	SWA	None	Died
2424	SWA	None	Died
2420	SWA	None	Recovered on Day 4
2413	SWA	None	Recovered on Day 20
2397	SWA	None	Recovered on Day 4
1667	SWA	None	Died
5584	SWA × Uit.	None	Recovered on Day 6
6168	SWA × Uit.	None	Died
6543	Zulu	None	Died
4456	Zulu	None	Died
4209	Zulu	None	Died
4160	Zulu	None	Died
4209	Zulu	None	Died
*B*8255	Uit.	Antibiotic	Died
*B*1204	SWA × Uit.	None	Died
*P*5689	Uit.	None	Died

B = Bovine
P = Pig

Field cases. Eight field cases of sweating sickness (7 calves and 1 sheep) were presented to the out-patients clinic of the Faculty of Veterinary Science, University of Pretoria, over a 2-month period in 1983. The diagnoses in all cases were confirmed on history, symptomatology and clinical pathology (Van Amstel, 1984).

* Compropen, Milvet
** Avi C & B Concentrate Special, Avima (Edms) Bpk., Reg. No. 1065

TABLE 4 The effect of hyperimmune serum on experimental cases of sweating sickness in sheep

Sheep No.	Tick strain	Donor No. and number of times challenged	Dose (mℓ) intravenously	Recovered on Day No.
3173	SWA	6522 /3	100	1
5120	SWA	*B*545 /2	100	3
4870	SWA	*B*545 /2	100	3
5683	SWA × Uit.	*B*8094/4	100	1
5892	Zulu	*B*8094/4	50	1
6235	SWA × Uit.	*B*8094/3	250	1
6204	SWA × Uit.	*B*8094/3	250	1
5823	SWA × Uit.	*B*8094/2*	50	1
3826	SWA	6522 /2	100†	1
3887	SWA	5654 /1	100	1
5575	Uit.	6522 /2	100†	1
5658	SWA	6522 /2	100†	1
4117	SWA	6522 /2	33#†	1
5654	SWA	6522 /2	50 § †	2
6174	Zulu	5683 /4	100	1
7507	SWA × Uit.	5683 /4	150	Died
6205	SWA × Uit.	*B*8094/3	250	1
5990	SWA	*B*8094/4	100	1
5970	SWA	*B*8094/4	100	1
6238	SWA × Uit.	*B*8094/3	250	1
6189	SWA × Uit.	5683/4	250	Died

B = Bovine serum
* Serum had been stored frozen at −18 °C for 3 months prior to use
\# 33 mℓ globulins precipitated using NH_3Cl from 100 mℓ serum was used
§ 50 mℓ serum was given on 3 consecutive days
† This serum was from a sheep which had been challenged 40 days prior to it being bled as a donor
Uit. Uitenhage strain of sweating sickness causing *H. truncatum*
SWA South West Africa strain
Zulu Zululand strain

TABLE 5 The effect of hyperimmune serum on experimental cases of sweating sickness in cattle

Bovine No.	Trick strain	Donor No. and number of times challenged	Dose mℓ intravenously	Recovered on Day No.
1201	SWA × Uit.	8094/4	500	3
1202	SWA × Uit.	8094/4	500	3
1203	SWA × Uit.	8094/4	250*	2
1205	SWA × Uit.	8094/4	150	1
1206	SWA × Uit.	8094/4	500*	4
8094	Uit.	*B*545/2	300	4
8053	Uit.	*B*545/2	450	Died
8159	Uit.	*B*545/2	400	Died

B = Bovine serum
* A total volume of twice the amount indicated of fresh blood collected in acid citrate dextrose was used

TABLE 6 The effect of hyperimmune serum on experimental cases of sweating sickness in pigs

Pig No.	Trick strain	Donor No. and number of times challenged	Dose mℓ intravenously	Recovered on Day No.
2369	Uit.	5689/3	25*	3
2373	Uit.	5689/3	100	1
2358	Uit.	5689/3	100	1
2026	Uit.	6204/2	100	1
2027	Uit.	5683/4	100	1

* 25 mℓ serum was given on 3 consecutive days

These animals were all treated with fresh blood or serum from hyperimmunized donors as well as with symptomatic and supportive treatment based on the clinico-pathological findings. Their response to treatment was monitored as described above.

RESULTS

Control sheep. Out of the 63 experimental control sheep 38 died and 25 recovered 4–5 days after the symptoms had reached a stage at which they could be confirmed as sweating sickness. The mortalities caused by the various tick strains differed: 21 out of 37 (57 %) challenged with the Uitenhage strain died, 8 out of 16 (50 %) challenged with the South West Africa strain, 1 out of 2 challenged with the SWA × Uitenhage strain and 5 out of 5 (100 %) challenged with the Zululand strain.

Experimentaly and field cases treated with hyperimmune serum only

Sheep. Of the 21 treated sheep, 2 died and 19 recovered within 1 or 2 days of treatment (Table 4).

No difference between the efficacy of serum taken from donors which had been challenged only once and that of serum taken from donors that had been challenged up to 4 times could be detected.

Sheep 5823, treated with serum which had been stored for 3 months at −18 °C, recovered as quickly as those treated with unfrozen serum. Sheep 4117, treated with precipitated globulins, also recovered within 1 day, Sheep 5654, which had been treated on 3 consecutive days with 50 mℓ of serum, showed signs of recovery only on the 2nd day of treatment. The first sign of recovery was the return to normal of the rectal temperature, if it

TABLE 7 The effect of hyperimmune serum together with symptomatic and supportive treatment on natural field cases of sweating sickness

Animal	Age (months)	Specific treatment	Dose mℓ intravenously	Result (recovered on Day No.)
Calf 1	2	Blood	500	5
Calf 2	2	Serum	100	5
Calf 3	1	Serum	200	2
Calf 4	6	Serum	500	3
Calf 5	3	Blood	500	7
Calf 6	3	Serum	100	4
Calf 7	6	Blood	400	4
Sheep	24	Serum	50	2

had been elevated. This was followed by the dissipation of the inflammation of the mucous membranes, a return of the appetite and a marked improvement in habitus. The inflammation of the skin disappeared leaving only dry crusty lesions where the skin had been easily scraped off during the acute phase of the disease.

Cattle. Of the 8 cattle treated 2 died and 6 recovered (Table 5). The effect of treatment followed the same pattern in cattle as for sheep. The process of recovery, however, extended over a period of 3–4 days.

Pigs. All 5 pigs treated recovered within 1–3 days of treatment (Table 5). The pigs which received a full dose of 100 mℓ serum lost all signs of skin and mucosal inflammation within 6 h and they began feeding again within 8 h. Only dry skin lesions, the traces of damage which occurred during the acute stages of the disease, were present after 12 h.

The pig that received 3 daily doses of 25 mℓ showed signs of recovery only after the 2nd dose was administered.

Cases treated with hyperimmune serum and antibiotics

All the field cases recovered within about 4–5 days (Table 7).

The dosage required for a 71 kg Ile de France ram was smaller than for the calves which ranged in mass from 30 kg–180 kg.

DISCUSSION

For the first time, hyperimmune serum has provided us with a useful and successful specific treatment for sweating sickness. It is clear from the results that the effect is best in pigs, very effective and dramatic in sheep and, although slower and not as dramatic, an essential part of the successful treatment of calves.

Sheep serum is effective in the treatment of the disease in sheep, cattle and pigs. Cattle serum was found to be effective in cattle and sheep but was not used in the treatment of cases of sweating sickness in pigs.

The mortality rate in sheep was reduced from 60 % to 9 %, with a dramatic increase in the rate of recovery. When one remembers that the 2 sheep that died died within 4 h of treatment, then the recovery rate is even more remarkable. Neitz (1959) reported a 95 % mortality in sheep with sweating sickness. The results of this trial, namely 60 % mortality in untreated cases, support the theory that mortality depends on the virulence of the strain of tick involved. This is further strengthened by the differences seen in the percentage mortality caused by the different strains used in this trial: Uitenhage 57 %, SWA 50 %, SWA × Uitenhage 50 %, and Zululand 100%. All the sheep in this trial came from a particular farm in the Barkly East area of the Cape Province and were all Merinos.

The poorer results in cattle are difficult to explain. In the experimental cases, the 2 cattle that died were treated with serum from Bovine 545 after it had been challenged only twice. There was no reaction to either challenge, and therefore the animal was assumed to be immune. The same serum was used on 2 sheep, and their recovery was slower than was experienced when other sera were used on sheep. It is possible that for some reason this donor was unable to produce a high enough antibody titre to the toxin.

The response of the field cases to treatment, both specific and supportive, was much better than that previously experienced, when only the supportive treatment was given.

Serum from sheep or cattle appeared to be equally effective. Cattle, however, because they are generally larger than sheep, would appear to be more practical as donors if large amounts of hyperimmune serum are to be produced.

The number of times the donor animal is challenged also appears not to be important, as no difference in the efficacy of serum of sheep challenged only once with ticks and that from animals challenged on numerous occasions, could be detected.

Serum from animals which had been challenged more than 6 weeks prior to their being bled as donors was not used. This was as we suspected, that after this period the levels of the antibody titre may no longer be sufficiently high. However, an investigation may be worthwhile as it may not be necessary to challenge animals as often if the titre remains high for longer periods.

The successful treatment of a sheep with serum that had been stored for 3 months at −18 °C indicates that the serum can be kept in this way without any deterioration in efficacy. Although only one animal was treated with precipitated immunoglobulins, the success of this treatment indicates that precipitated immunoglobulins can be used in order to save storage space.

Treatment with fresh blood was successful in 3 cases. Where this method is possible, it is the method of choice, as the blood is in itself a good supportive treatment.

Contrary to expectations, the dosage of hyperimmune serum required for cattle is greater than that required for sheep and goats. This does not depend on the size of the diseased animal, as in some cases the sheep treated were heavier than the calves.

A minimum dosage of 25 mℓ given on 3 consecutive days is required in pigs. A dosage of 50 mℓ was effective in sheep on 2 occasions, while a 100 mℓ dose given once gave consistently good results. In the experimental cases, calves required at least 150 mℓ. Together with supportive and symptomatic treatment in the natural field cases, a minimum of 100 mℓ was required. These dosages, however, are only estimates as, to date, there is no serological test by which the titres of various serum samples can be tested. The method of Stone, Neish & Wright (1982) could possibly be adapted for this purpose.

We conclude, therefore, that the use of hyperimmune serum as specific treatment, in conjunction with supportive and symptomatic treatment based on the clinical pathology, is an essential part of the treatment of sweating sickness.

There are various practical means of production. A single bovine of about 400 kg could be challenged and bled (4 ℓ) safely every 6 weeks if it was kept on a good plane of nutrition. This would give 16 ℓ serum or 64 doses per year. The serum could then be stored frozen or

kept, also frozen, as a globulin fraction until it was needed. At smaller laboratories, or even at veterinary clinics in the rural areas, a sheep could be kept to provide about 16 doses per year. In areas where such facilities are unavailable, the practitioner could bleed an animal on the affected farm, particularly if it has a history of sweating sickness. The possibility of an older animal having antibodies would depend on the enzootic situation on that particular farm. The serum or blood, even without the desired antibody, would be beneficial as supportive treatment.

Our findings also create the possibility of producing a commercial immunoglobulin in freeze-dried form.

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