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DEVELOPMENT OF A PROPHYLACTIC REGIME USING TERRAMYCIN/LA TO ASSIST IN THE INTRODUCTION OF SUSCEPTIBLE CATTLE INTO HEARTWATER ENDEMIC AREAS OF AFRICA

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ABSTRACT

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As a result of a personal survey in 1982, interviewing veterinarians from Louis Trichardt to Uitenhage, it was concluded that bovine heartwater is currently regarded as the most serious tick-borne disease problem in South Africa. A combination of long-acting oxytetracycline and prednisolone is regarded as the most effective therapy. The disease is almost inevitable in unprotected young high-grade susceptible stock introduced into endemic areas such as the northern Transvaal and the Valley Bushveld of Natal and the Eastern Cape. A series of trials was conducted at Settlers, Pietermaritzburg and East London on farms representative of these areas and it was demonstrated that 4 injections of 20 mg/kg of long-acting oxytetracycline on Days 0, 7, 14 and 21 after introduction enabled such stock to be introduced without the disease occurring. A further trial was carried out on the Pietermaritzburg farm, where it was shown that the number of injections could be reduced to 3, on Days 7, 14 and 21 or Days 7, 12 and 17, or even 2 on Days 7 and 14. Two points need stressing. First, these results were obtained in areas of high heartwater endemicity. Second, in order to be confident that the regime will be effective it is necessary to have acquired knowledge of the epidemiology of the disease at the farm. Thus in the 2nd year at Pietermaritzburg we were able to use a reduced treatment regime because we knew the pattern of disease occurrence.

Problems are perceived for the large scale introduction of such a prophylactic regime, namely: (1) a 100 % challenge must occur in the first 4 weeks of exposure; (2) immunologically distinct strains of heartwater may occur on the same farm at different times of year; (3) the duration of immunity acquired as a result of the regime has not yet been established, and (4) the attritive *Theileria mutans*-type pathogen which is very common in South Africa may cause breakdowns in heartwater immunity.

Since oxytetracycline is known to be active against all major tick-borne pathogens of cattle, and even apparently against the ticks themselves, some form of prolonged administration of the drug could be used to overcome the problems enumerated above.

INTRODUCTION

In 1981 I was fortunate in being able to attend the meeting on Tick Biology and Control organised by the Tick Research Unit, Rhodes University, and to hear the paper on control of heartwater in Angora goats by Brian Gruss, who was practising in Uitenhage at the time (Gruss, 1981). His approach when introducing goats into a heartwater endemic area was to give them a series of subcutaneous (s.c.) or intramuscular (i.m.) injections of 3 mg/kg of oxytetracycline (50 mg/mℓ) on Days 10, 20, 30, 45 and 60 but not to dip them until Day 60. This paper prompted me to see if a similar approach could be used to introduce susceptible cattle into heartwater endemic areas of South Africa.

This paper consists of 2 parts. In the first a description is given of a survey that I carried out in 1982, with the help in Natal of our Pietermaritzburg field unit, to discover the relative importance of heartwater within the area of incidence delineated by Howell, Walker & Nevill (1978). In the 2nd part the results of field trials at sites in the Transvaal, Natal and Eastern Cape, selected during the survey, are briefly described. In these trials we attempted to introduce susceptible calves into heartwater areas while protecting them with a series of injections of long-acting oxytetracycline[1]. Finally, some conclusions are drawn from the work, and possible ways in which our experience may be of value in further investigations in the prophylactic control of heartwater are suggested.

When deciding the direction which the survey should take 2 assumptions were made: (1) Heartwater in cattle is economically more important than it is in sheep or goats. (2) The main problem areas for tick-borne disease in South Africa coincide more or less with the distribution of the heartwater vector *Amblyomma hebraeum* as delineated by Howell, Walker & Nevill (1978). Since I wanted to start my research programme in October 1982 I saw as many large animal veterinarians as possible in the E. Cape and Transvaal during a visit in July 1982, and also met with my Pietermaritzburg team to see what they had discovered in Natal. We used the same questionnaire as the basis for interviews with a total of 24 veterinanrians. Basically we asked if they dealt with heartwater in cattle in their practice and, if so, in which animals and at what time of year did it occur, and how did they rate its importance in their practice compared to redwater and anaplasmosis.

The results of the survey are summarized in Fig. 1. The distribution of *A. hebraeum* is shown as a shaded area, and the numbers represent towns where veterinarians were interviewed. The pie charts for the Transvaal, Natal and the E. Cape are divided to show the overall relative importance of the 3 tick-borne diseases, the most important according to each veterinarian being scored 3, the next 2 and the least 1. In the eastern Transvaal redwater was regarded as being of equal importance to heartwater in cattle. Elsewhere in the Transvaal, though, heartwater was judged as the most important tick-borne disease of cattle. In Natal, redwater was the most important, and heartwater was not regarded as a problem at Ixopo, Pietermaritzburg or Howick. Anaplasmosis was thought to be the most important tick-borne disease at Estcourt. In the E. Cape, as in several parts of Natal, heartwater was judged to be a major problem in Valley Bushveld. The Kei River valley was singled out as being an area of high endemicity and the bushveld on the coastal plain was identified as a danger area. At Queenstown anaplasmosis was identified as the most important disease, and redwater was generally reckoned to be a significant problem elsewhere.

Most cases of heartwater occurred in susceptible introduced stock, but home-bred animals, notably calves of 6–8 months, were also vulnerable if unprotected by vaccination. The peak period for heartwater was the summer, particularly December to February.

All the veterinarians consulted treated heartwater with oxytetracycline and many also used a cortisone drug

[1] "Terramycin/LA", Pfizer

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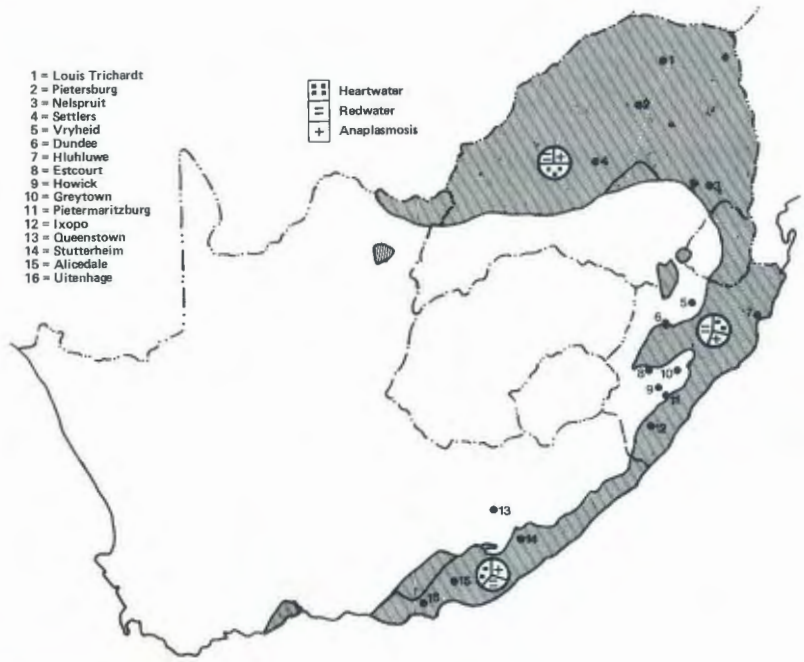

FIG. 1 Tick-borne disease survey in South Africa 1982.
Correlation between importance of Heartwater and distribution of *Amblyomma hebraeum* (shaded)

such as prednisolone[2], a diuretic, and in acute cases a sedative to counteract extreme nervous symptons. Although long-acting oxytetracycline was the drug of choice in many cases, a number of veterinarians were under the impression that therapeutic drug levels were reached more quickly with an intravenous (i.v.) injection of a short-acting oxytetracycline[3,4].

As a result of the survey I found willing collaborators in Lente van der Merwe at her farm at Settlers, in the northern Transvaal, and Johann Schröder at the SABS farm near East London in the E. Cape. The farm just outside Pietermaritzburg which we used as an experimental facility was an ideal representative of Natal Valley Bushveld.

Materials and Methods

It had been established that calves introduced from heartwater-free areas were especially susceptible to the disease. Thirty-six Friesland heifer calves were therefore purchased for Settlers from a tick-borne disease-free farm in the Orange Free State; 36 and 40 Friesland bull calves from a similar farm on the highveld in South Natal for Doornhoek farm, Pietermaritzburg, and 34 Hereford-Afrikaner cross calves from a farm on the highveld near Sterkstroom, E. Cape for Little Go farm, East London. All these animals were screened for heartwater antibodies before purchase, using the indirect fluorescent antibody test.

In the first series of trials the animals were moved to the farms, mass-measured, ranked and distributed to equal groups. At Settlers, 12 calves were untreated controls, 12 received a series of injections of 20 mg/kg of long-acting oxytetracycline i.m. in the rump on Days 0, 7, 14 and 21 after introduction, and 12 received similar injections on Days 0, 14 and 28. The same design was used at Doornhoek, but at Little Go 2 groups of 17 calves were used, 1 group being untreated controls, and the other receiving the 4 injection regime (Days 0, 7, 14 and 21). The animals were not treated with acaricide for the first 28 days of exposure at Settlers and Doornhoek, but owing to the high tick challenge at Little Go regular spraying with amitraz[5] at 0,025 % began there on Day 14. Rectal temperatures were taken regularly in the early morning in the crush at each trial site, and adult ticks were counted either weekly or fortnightly. If any animal had a febrile response (temperature 40 °C or more) blood smears were taken and Giemsa-stained so that they could be examined for haemoparasites. Clinical heartwater was treated with 20 mg/kg of long-acting oxytetracycline i.m. plus 0,5 mg/kg of cortisone i.m., and redwater was treated either with imidocarb diproprionate[6] or diminazene[7] at the recommended dose rate. If animals died, a post-mortem was carried out whenever possible and brain smear biopsies made and Giemsa-stained to detect *Cowdria ruminantium* organisms. Observations on the trial animals continued for 3 months.

Results

The reactions of the animals during the initial 35 days of the exposure period are summarized in Table 1.

At Settlers, there was a very severe challenge of both heartwater and redwater (*Babesia bigemina* infection), with a total of 10 untreated animals contracting heartwater and 9 contracting redwater. The symptoms of redwater appeared first, followed by those of heartwater. At Doornhoek, the challenge was of heartwater alone and all 12 untreated controls contracted the disease by Day 26 of exposure. At Little Go there was a mixed challenge of heartwater and both forms of redwater (*B. bigemina* and *B. bovis*), and 6 of the untreated controls died during the initial bout of heartwater. All those that survived contracted redwater immediately afterwards, 6 more of them dying.

In contrast to the severe clinical episodes in the untreated control animals, virtually all the calves that had the 4 injection drug regime survived the 'primary' exposure period unscathed, but several of those that had

[2] "Delta Cortril", Pfizer
[3] "Miltet", Milvet
[4] "Liquamycin 100", Pfizer
[5] "Triatix Cattle Spray (Mo)", Coopers Animal Health
[6] "Forray-65", Coopers Animal Health
[7] "Berenil", Hoechst

TABLE 1 Clinical reactions of tick-borne disease suceptible calves during first 35 days at Settlers, Doornhoek and Little Go

Farm	Treatment	No. of animals	Animals with clinical disease				
			Heartwater + redwater	Heartwater	Redwater	Mean days to symptons (range)	
						Heartwater	Redwater
Settlers	Control	12	7	3	2	25,2(23–27)	18,3(15–22)
	TM/LA 0, 7, 14, 21	12	0	0	1	—	17
	TM/LA 0, 14, 28	12	0	0	6	—	16,5(15–20)
Doornhoek	Control	12	—	12	—	19,3(14–26)	—
	TM/LA 0, 7, 14, 21	12	—	2	—	16,0(15–17)	—
	TM/LA 0, 14, 28	11	—	5	—	13,2(10–16)	—
Little Go	Control	17	11	6	0	24,9(22–28)	31,0(27–33)
	TM/LA 0, 7, 14, 21	17	0	0	0	—	—

only 3 injections at fortnightly intervals had either clinical heartwater (at Doornhoek) or redwater (at Settlers). The tick challenge at both Doornhoek and Little Go was heavy, as was anticipated, since the animals were encourage to move through the Valley Bushveld. At Settlers the tick challenge was moderate.

During the succeeding 2 months' observation periods at each farm, several animals had secondary episodes of heartwater or redwater. At Settlers such problems occurred only in the animals that had received 3 injections of long-acting oxytetracycline. In the bushveld, breakdowns of acquired immunity could frequently be linked with a general loss in condition of the animals owing to the combination of chronic *Theileria mutans*-type infection and poor nutrition.

Encouraged by the results of these trials, a 2nd trial was carried out at Doornhoek farm, once again starting in the spring, when the tick numbers were increasing rapidly. In this trial we took into account the knowledge gained from our previous trial which had shown that untreated animals would first show symptoms of heartwater between Days 14 and 26 after exposure. We therefore reduced the number of injections of long-acting oxytetracycline to 3 (on Days 7, 14 and 21, or Days 7, 12 and 17) or 2 (on Days 7 and 14) on the theory that the critical period of drug cover would be Days 7–19. The results were so clear-cut that a table is unnecessary. All 10 untreated control animals contracted clinical heartwater between Days 14 and 29 (mean 20,8) and 6 of them died despite therapy. In contrast, no symptoms of heartwater were detected in treated animals during the 35 day exposure period, although intermittent febrile episodes occurred in all the animals.

Discussion

These results appear to be very encouraging for further development of a prophylactic strategy for the introduction of susceptible cattle into tick-borne disease endemic areas. The parallel experiments in Kenya against the notorious pathogen *Theileria parva,* causative organism of East Coast fever, also give rise to optimism (Chumo, Irvin, Morzaria & Purnell, 1987).

There are, however, several pointers for further research and development. Firstly, the success of this strategy depends on a high level of disease challenge during the primary exposure period when the animals are under drug cover. If the challenge is not 100 % unchallenged animals have no opportunity to build up immunity and remain fully susceptible to subsequent challenge. In this respect it is clear that the use of a living vaccine, be it blood or tick-derived, and a blocking dose of drug ensures that the disease challenge has occurred. Secondly, it is by no means certain that the strain of heartwater which is carried by spring ticks is identical to that carried by, say, autumn ticks, which may conceivably have fed in the interim on wild animals which could be reservoirs of infection. So the natural immunity acquired in the spring may not protect against alien strains later in the season. Thirdly, it is uncertain how long animals which have acquired immunity to heartwater in this way are protected against homologous strain challenge. This must depend on seasonal fluctuations in challenge levels and also on the robustness of immunity in older animals of different breeds. Fourthly, there is evidence from 2 of the trial sites that the *T. mutans*-type pathogen found there can cause breakdowns in the immunological defences of animals, and that recrudescences of both heartwater and redwater occur in animals which should be immune as a result of earlier disease challenges. My observations on other trial sites suggest that this pathogen is rather underestimated in South Africa, and, indeed, in sub-Sahelian Africa in general.

These, therefore, are 4 factors which prevent such regimes being recommended for general use at this stage. Further examination of the factors may result in reassurance that some of them are unimportant when a prophylactic regime is used. However, there is another recently developed approach which could be used in the control of the disease, i.e. extended delivery technology, an example of which is an orally-administered morantel sustained-release bolus for the prophylactic control of parasitic gastroenteritis (Jones, 1981). During the coming decade further developments from our own, and other research laboratories will clearly lead to new and improved delivery systems for a wide variety of agents against disease and agents for growth. In oxytetracycline, we have a drug known to be active against *Theileria, Babesia, Anaplasma* and *Cowdria* and even possibly against the symbiotic rickettsiae necessary for the successful survival of ixodid ticks themselves (Purnell, Gunter & Scröder, 1987). It may be possible to develop a sustained delivery dosage form which will release protective levels of the drug for long enough to provide an effective control method.

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