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CHEMOTHERAPY OF *THEILERIA PARVA LAWRENCEI* INFECTIONS IN CATTLE WITH HALOFUGINONE

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ABSTRACT

DE VOS, A. J. & ROOS, J. A., 1983. Chemotherapy of *Theileria parva lawrencei* infections in cattle with halofuginone. *Onderstepoort Journal of Veterinary Research*, 50, 33–35 (1983).

Halofuginone lactate, given once orally at a dosage rate of 1,2 mg/kg body mass on the 1st, 3rd or 5th days of fever, resulted in the recovery of only 1 out of 5 splenectomized cattle. Three splenectomized animals, treated on the 1st as well as the 4th day of fever, recovered and were then carriers. Six untreated controls all died. The potential value of a chemotherapeutic agent for *Theileria parva lawrencei* infections in South Africa is discussed.

INTRODUCTION

With the eradication of East Coast fever (*Theileria parva parva* infections) from South Africa (Anon., 1981), theileriosis has assumed a less important role as a cause of stock losses in this country. Corridor disease (*Theileria parva lawrencei* infection), however, is still a significant cause of mortality, despite the restriction of the movement of buffalo (*Syncerus caffer*) by means of fences around the game reserves involved (Bigalke, De Vos & Barrowman, 1976). Thus, during the summer of 1980/81, 3 outbreaks of Corridor disease were reported on farms adjoining or near the Kruger National Park, Transvaal. A total of 8 farms were involved and at least 135 cattle are known to have died (L. R. Hurter, 1981, personal communication). Buffalo were known to have been involved in each outbreak.

One of the affected farmers attempted prophylactic treatment with tetracyclines, but still lost most (26) of the diseased animals. The value of a drug that can be used as a curative in clinically affected animals is therefore obvious.

During the past 7 years significant progress has been made on the chemotherapy of bovine theileriosis (Brown & Masiga, 1981; Dolan, 1981). Currently, 2 compounds, namely, 993C* (a naphthaquinone) and halofuginone** (a quinazolinone) have been singled out for development (Brown & Masiga, 1981)

The effect of halofuginone against *T. p. parva* has been reported by Schein & Voigt (1980; 1981). In addition, Uilenberg, Jongejan, Perié & Franssen (1980) reported the efficacy of this compound *in vitro* against *T. p. lawrencei*.

The purpose of this paper is to report results obtained at this laboratory on the effect of halofuginone against tick-induced infections of *T. p. lawrencei*.

MATERIALS AND METHODS

Animals

Only splenectomized *Bos taurus* cattle, born and raised under tick-free conditions at this laboratory, were used.

Theileria *infection*

All the animals were infected with a tick-transmitted isolate of *T. p. lawrencei* originating from the Hluhluwe Game Reserve, Natal and designated Isolate 3 (De Vos, 1982). This isolate has been maintained in the laboratory by tick passages between cattle and is not transformed.

Evaluation of reactions

Thin blood smears from the tip of the tail were prepared daily after tick infestation until death or recovery. In recovered animals thin smears were made 3–5 times a week for 3–5 months from 28 days after infection. The smears were stained with Giemsa's stain and examined for macroschizonts and piroplasms.

Parotid lymph nodes were palpated daily after tick infestation and thin smears prepared of biopsy material when they were noticeably enlarged. These smears were then stained as above and examined for schizonts.

Macroschizont index (MSI) determinations were made in lymph node biopsy smears and in blood smears according to the method of Jarrett, Crighton & Pirie (1969). A linear count was made of 1 000 lymphoid cells and their associated macroschizonts, both intracellular and extracellular. The result was expressed as a percentage. The MSI of each animal was determined daily, starting on the day of treatment.

The "incubation period", as defined in this study, was the interval between the infestation of an animal with infected ticks and the first rise in its rectal temperature above 39,4 °C. The temperatures were recorded daily between 08h00 and 09h00.

"Febrile reactions", as used in this study, indicated the total period in days during which the rectal temperature of an infected animal was elevated above 39,4 °C.

Chemotherapy

Ticks known to be infected with Isolate 3 were used to infect 8 splenectomized animals. When the animals reacted, they were treated with halofuginone lactate at 1,2 mg/kg (1 mg/kg halofuginone base), as suggested by Schein & Voigt (1980). The drug was dissolved in 500 mℓ of water and administered as an oral drench. Five cattle were treated once only, either on the 1st day of fever (2 animals), the 3rd day of fever (2 animals) or the 5th day of fever (1 animal) (Table 1). The remaining 3 animals were treated twice, namely, on the 1st and 4th days of fever (Table 1), as suggested by Bauer (personal communication, 1981). A further 6 animals were infected and acted as untreated controls (Table 1).

RESULTS

Out of the 5 animals treated once with halofuginone at 1,2 mg/kg, only 1 survived, while all 3 animals treated twice at the same dose rate recovered (Table 1). All 6 untreated controls died or were slaughtered *in extremis*.

The drug had a marked effect on the macroschizonts, as the MSI's of the animals on the days following treatment showed. The mean MSI of the 5 animals treated once only was 3,4% on the day of treatment. It decreased to 2,2%, 1,5% and 0,6% during the 3 days following therapy, but increased again to 2,2% and 4,5% during the next 2 days before death or recovery. In the 3 animals treated twice, no schizonts were seen for 10–14 days after the 2nd treatment, but they then reappeared for 1–3 days in very small but detectable numbers (MSI<0,1%) in blood smears of all 3 animals. In the 6 untreated cases, the MSI's remained at relatively constant levels with a mean of 3,9% at the time of death.

Piroplasms were seen in the blood smears of 3 out of the 4 recovered animals and were first detected 25–28 days after tick infestation. The piroplasms persisted in very low (<0,01%) numbers for the duration of this study (3–5 months).

* Wellcome

** Hoechst

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TABLE 1 The efficacy of halofuginone lactate against *T. p. lawrencei* infections in splenectomized cattle when given orally at 1,2 mg/kg

Animal No.	Incubation period*	Days of treatment	Reaction		Outcome
			Schizonts	Piroplasms	
Treated once on:					
B4023	11	11	+	–	Died Day 18
B4336	10	10	+	–	Died Day 19
B3346	11	13	+	–	Recovered
B3407	11	13	+	–	Died Day 19
B2635	10	14	+	–	Died Day 21
Treated twice on:					
B3353	12	12&15	+	+	Recovered
B4246	12	12&15	+	+	Recovered
B9140	13	13&16	+	+	Recovered
Untreated controls:					
B0124	11	–	+	–	S.I.E.**Day 17
B3409	10	–	+	–	S.I.E. Day 14
B4443	12	–	+	–	S.I.E. Day 18
B3463	12	–	+	–	Died Day 17
B9227	12	–	+	–	Died Day 18
B9056	16	–	+	–	Died Day 19

* Day of first temperature rise (>39,4°C)

** S.I.E. = Slaughtered *in extremis*

In 2 of the animals treated once only, febrile reactions persisted until death. In the remaining 3 animals. temperatures returned to normal within 2–3 days, but increased again to levels above 39,4 °C 2–8 days later and remained elevated until death or recovery.

The body temperatures of the 3 animals treated twice were normal on the day after the 2nd treatment and remained normal for 3–6 days. Second fever reactions followed that persisted for 5, 11 and 13 days, respectively, but all 3 animals recovered.

DISCUSSION

Schein & Voigt (1980) reported the efficacy of halofuginone in cases of East Coast fever (*T. p. parva* infection). They infected 8 cattle with lethal doses of a *T. p. parva* stabilate and treated 4 of them with 1,2 mg/kg body mass of halofuginone as soon as the first clinical symptoms were visible, that is, when the body temperature rose above 40 °C. Lymph nodes were enlarged and schizonts were demonstrated in lymph node biopsies. Within 48 h of the oral application all the animals had normal temperatures. No schizonts were detected after 3–4 days, and recovery was complete. A further 2 animals were not treated "until they were close to exitus". Within 24 h after these animals had received 1,2 mg/kg halofuginone orally, their temperatures were normal and the number of schizonts was reduced. No schizonts were detected 4–5 days after treatment and recovery was uneventful. Two untreated controls died 16 and 21 days after infection, respectively. Similar results were subsequently reported by Schein & Voigt (1981). Voigt & Heydorn (1981) also reported that 7 calves infected with *T. p. parva* were successfully treated with halofuginone, given once at 1,2 mg/kg. Body temperature had returned to normal after 48 h and no schizonts were detected after 3–4 days.

It would appear, therefore, that Isolate 3 of *T. p. lawrencei* used in this study was more virulent or, alternatively, more resistant to treatment than the Muguga strain of *T. p. parva* used by Schein & Voigt (1980; 1981) and Voigt & Heydorn (1981). The recrudescences seen after treatment in the present study are similar to those reported by McHardy & Morgan (1981) and Morgan & McHardy (1982) in their observations on animals infected with *T. p. parva* (Muguga). They reported moderate to severe recrudescences in cattle treated once with halofuginone during the early or late stages of the infection.

From these preliminary observations it is evident that drugs such as halofuginone will have great application in outbreaks of Corridor disease. The carrier state demonstrated in 3 out of the 4 recovered splenectomized animals in this study is a well-known phenomenon that was first demonstrated by Neitz (1958). Whereas Corridor disease traditionally kills a very high percentage of affected animals (Neitz, 1957), the use of drugs such as halofuginone may alter the situation considerably. It is therefore imperative that the ability of recovered intact animals to act as carriers infective for ticks be determined for South African strains of *T. p. lawrencei* before large scale treatment is allowed during outbreaks.

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