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Chemotherapy of field cases of East Coast fever using halofuginone lactate

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Summary

The chemotherapeutic effect of halofuginone lactate (Terit, Hoechst) was tested against natural pathogenic *Theileria parva* infections (East Coast fever, ECF) in 24 cattle. Halofuginone lactate, administered per os, 1.2 mg per kg b.wt and repeated after 48 h manifested a potent schizonticidal effect, observed between 5 and 11 days post treatment. Disappearance of erythrocytic forms (EF) took long, ranging from 6 to 34 days post treatment. Differences on efficacy between halofuginone lactate tablets and solution were not observed. The use of furosemide (Dimazon, Hoechst) to promote diuresis in pulmonary oedema and streptomycin sulphate for control of secondary pulmonary infections, as supportive therapy measures, enhanced recovery from ECF. A recovery rate of 96% was recorded. Relapses were not observed.

Key words: cattle; East Coast fever; *Theileria* schizonts and erythrocytic forms; halofuginone lactate; dimazon; streptomycin sulphate; supportive therapy.

Introduction

Theileriosis, and in particular East Coast fever (ECF), causes the greatest losses among cattle in Tanzania (Mkonyi, 1984). *Rhipicephalus appendiculatus* is the only natural vector of *Theileria parva* in eastern and southern Africa (Uilenberg, 1976). Other species of ticks have been proved to be capable of transmitting ECF experimentally but play no significant role in nature (Barnett, 1968).

Considerable effort has been made toward the search of an effective drug in the treatment of theileriosis. Tetracyclines have some prophylactic effect in the early stages of the infection, but their curative use in the treatment of the clinical disease is limited (Radley et al., 1975).

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The antitheilerial action of menoctone as a potent antischizont drug was reported by McHardy et al. (1976). The antitheilerial effect of an analogue of menoctone, the Wellcome compound 993C presently marketed as Clexon, was reported by Dolan (1981). Further studies of this compound by Morgan and McHardy (1982) revealed severe damage on both *Theileria parva* schizonts and piroplasms, with the latter remaining mostly pycnotic. Schein and Voigt (1979) reported the antitheilerial effect of the anticoccidial halofuginone, enhanced by its antipyretic properties.

The first preliminary report on the chemotherapy of bovine theileriosis with halofuginone in Tanzania was reported by Njau and Mkonyi (1981). Halofuginone was found to be effective against theileriosis. Degeneration of schizonts was noted. Latest report on the treatment of field cases of ECF in Tanzania with halofuginone lactate by Njau et al. (1985), records 100% recovery rate for early treated cases against 36% for cases diagnosed and treated late. In the present paper, we report further studies on the chemotherapy of ECF using solution and tablet forms of halofuginone lactate, supplemented by supportive therapy.

Materials and Methods

Location. Treatment trials were conducted in parts of Coast and Dar es Salaam (DSM) regions, situated within easy reach of the Animal Diseases Research Institute (ADRI) DSM. The climate in the above mentioned areas favours the development and survival of *R. appendiculatus*.

Cattle. Suspected cases of ECF in cattle were reported to ADRI by veterinary personnel and farmers, during the period of July, 1984 to September, 1985. All cattle were Zebu crosses, aged 6 months to 5 years. One cow was in late pregnancy (8½ months). Regular tick control by spraying with toxaphene emulsion at weekly intervals, and antihelminthic and trypanocides administration of experimental cattle were observed.

Drugs. – a) Halofuginone lactate (Terit-derivative of Stenorol, Hoechst) dl-trans-7-bromo-6-chloro-3-3- (3-hydroxy-2-piperidyl) acetonyl-4 (3H)-chinazolinon-hydrolactate was used to treat confirmed *Theileria parva* infections. – b) Furosemide (Dimazon, Hoechst) 4-chloro-N-furfuril-5-sulphamonyl-anthranilic acid, injectable, as 2, 2 iminodietanol salt was used where necessary to enhance diuresis or saluresis in pulmonary oedema. – c) Streptomycin sulphate was given to control secondary pulmonary infections; was chosen on the basis that it has no known therapeutic effect on *Theileria* parasites. – d) Imidocarb dipropionate (Imizol, Cooper) was used to treat concurrent anaplasmosis.

Parameters. Rectal temperatures and lymph node smears were taken daily from day 0 (day of treatment) until temperature dropped to normal (39.5) and macroschizonts disappeared in lymph node smears, then later as found necessary, until *Theileria parva* erythrocytic forms (EF) disappeared in peripheral blood smears. Blood and lymph node smears were air dried, fixed in methanol, and stained with Giemsa.

Parasites. Demonstration of "fairly numerous" macroschizonts (associated with active lymphocytosis) in lymph node smears, accompanied by elevation of temperature above 39.5°C, were regarded as obvious signs of ECF.

Experimental design. Cattle were divided into 2 groups of 13 and 11 each. The first group received halofuginone tablets and the second one was given the solution form; for subsequent evaluation of their efficacy. In addition to halofuginone treatment, 13 animals (10 from group 1 and 3 from group 2 = early infections) received supportive, streptomycin therapy, while 11 animals (3 from

group 1 and 8 from group 2 = advanced infections) received streptomycin and dimazon. Halofuginone lactate was administered per os, 1.2 mg per kg b.wt, and repeated after 48 h, in early and advanced stages of infection. A case was regarded as advanced if 1% or more of the red blood cells (RBC) were invaded by *T. parva* EF, and respiratory distress pronounced. A third dose was administered when found necessary. Streptomycin sulphate was given at the same time as halofuginone at a dose rate of 10 mg per kg b.wt, intramuscular (i/m) for 4 consecutive days. Dimazon was administered at a dose rate of 1 mg per kg b.wt, i/m, for 3 consecutive days. Criteria for recovery were disappearance of macroschizonts in lymph node smears and sustained drop of body temperature to normal.

Results

Out of the 24 treated cattle 23 recovered (recovery rate of 96%). One cow died of acute ECF with typical signs of theileriosis (Cowdry and Danks, 1933), on day 2, before receiving a full course of halofuginone. A sharp decrease in milk production (almost to zero in severe cases) and body weight were observed. Subsequently, milk production increased slowly, reaching original levels not earlier than 3 weeks post recovery. No obvious signs of drug toxicity were noticed. In the course of treatment and recovery from ECF 3 animals (12.5%) developed concurrent anaplasmosis, which was effectively treated with imizol.

Depending on severity of the infection, an initial drop of rectal temperature to normal was observed in the majority of cases 24 h post treatment. However, elevation of temperature was noted again later (48 h post treatment), before finally dropping to normal 6 days after treatment. In a few cases, temperature dropped 24 h after treatment, although not to normal levels.

Halofuginone showed a schizonticidal effect clearing the schizonts as early as days 5 to 11 post treatment. It cleared above 75% schizont parasitosis in 2 animals. Halofuginone seemed to have a limited effect against the EF. Disappearance of the latter took long, beginning day 6 to day 63 post treatment. Appearance of EF was, however, not observed where animals had received full course of halofuginone before the red blood cells were invaded. Whereas the disappearance of macroschizonts was preceded by a sustained drop of body temperature to normal, occurrence of the EF was irregular. Recrudescence of parasitosis was not observed. Likewise, differences on efficacy between the solution and tablet forms of halofuginone lactate were not noticed.

Discussion

The stage of the disease at which treatment is instituted is important. Many of the failures encountered in the treatment of ECF, particularly in advanced stages, have been associated mainly with the irreversible condition of the pulmonary oedema. The inclusion of dimazon in advanced stages of the disease and streptomycin in early and advanced stages of the infection, as supportive therapy measures, was significant in achieving the recovery rate of 96%. Njau et al. (1985) working on similar trials in Tanzania recorded a recovery rate of 36% in cases diagnosed and treated late (schizont parasitosis beyond 10% and EF

parasitaemia up to 25%). They did not incorporate supportive therapy. In the present trials where supportive therapy has been employed, all animals that received full course of halofuginone recovered, in spite of a schizont parasitosis of up to 75% and EF parasitaemia of up to 50%.

Toxicity studies were not conducted. However, results obtained from one cow show that halofuginone could be used to treat ECF even in pregnant animals. This cow received a total dose of 4.3 mg per kg b.wt of halofuginone lactate within the first 48 h of treatment. Important signs of toxicity such as profuse diarrhoea, cachexy and a purulent eye discharge were observed by Uilenberg (1980) after treating theileriosis in cattle with halofuginone 3 mg per kg b.wt, were not observed in this study. Early work was done with halofuginone hydrobromide which was much more toxic than halofuginone lactate which we used.

Observation on milk production from one cow following treatment of ECF with halofuginone shows that depending on severity of the infection and in the absence of other factors, the original (before illness) milk production record could be attained from the third week onwards post recovery.

Information on the exact effect of halofuginone on *Theileria* schizonts and EF is limited. Schein and Voigt (1979) reported disappearance of Koch bodies 72 h after single administration of a therapeutic dose while EF which were already present in blood smears on day of treatment, persisted for over 3 weeks. The authors of the present trials have recorded disappearance of schizonts between 5 and 11 days (Table 1) post treatment with halofuginone while EF slowly disappeared (6–34 days post treatment). One case had a very low EF parasitaemia extending over 63 days (schizonts had disappeared by day 6 post treatment, rectal temperatures and appetite were normal). The present results are comparable to those reported by Uilenberg et al. (1980), which described halofuginone 1–2 mg per kg b.wt, as a potent schizonticide on *T. p. parva* and *T. p. lawrencei*. The drug did not appear to be very active against the piroplasms of *T. p. parva*.

A marked drop of body temperature from 41.6 °C on day of treatment to 39.2 °C 24 h later was observed in one animal. Rectal temperatures rose again 72 h after treatment and fluctuated between 39.8 and 40.3 °C for 5 days before finally dropping to normal 8 days after treatment. Comparable observations were noted in other animals. The antipyretic effect of halofuginone as observed in the present trials are comparable to those recorded by Morgan and McHardy (1982). The authors observed a fall of rectal temperatures below 39.5 °C in all 5 treated cattle with halofuginone but then rose again to a mean peak of 40.7 (40.1–41.0 °C) about 6 days after treatment, before falling to normal about 10 days after treatment.

The clinical features of ECF, severity of the disease and the outcome are closely related to the parasite load, particularly macroschizonts (Irvin and Mwamachi, 1983). Provided the state of pronounced pulmonary oedema has

Table 1. Chemotherapy of East Coast fever with halofuginone

Day	Mean temperature (°C) ± SD				Range			
	HT		HS		HT		HS	
0	40.4±0.5		40.8±0.59		0.7		1.6	
5	39.6±0.27		39.8±0.32		0.7		1.1	
6	39.2±0.45		39.4±0.34		1.4		0.9	
8	39.1±0.38		39.3±0.44		1.0		1.5	

Mean No of animals with/without schizonts in lymph node smears									
PNS		(+) ^{sz}		+ ^{sz}		++ ^{sz}		+++ ^{sz}	
HT	HS	HT	HS	HT	HS	HT	HS	HT	HS
0				8/13	3/11	2/13	1/11	3/13	7/11
5	1/10	7/13	6/10	4/13	2/10	1/13		1/13	1/10*
6	7/13	8/10	6/13		1/10		1/10		
8	11/13	10/10	2/13						

Mean No of animals with/without erythrocytic forms (EF)									
PNS		(+)		+		++		+++	
HT	HS	HT	HS	HT	HS	HT	HS	HT	HS
0	2/11	8/13		2/13	1/11			3/13	8/11
5	2/10	7/13	1/10	3/13			2/10	3/13	5/10*
6	3/10	8/13	2/10	2/13			1/10	3/13	4/10
8	1/13	5/10	9/13		2/10	3/13	3/10		

(+) = Rare *Theileria* EF and schizont parasitosis

+ = Less than 1% of the red blood cells (RBC) parasitized

++ = 1% or more but less than 10% of the RBC parasitized

+++ = 10% or more of the RBC parasitized

+^{sz} = Fairly numerous

++^{sz} = Numerous

+++^{sz} = Very numerous

} schizonts

PNS = Parasites not seen

HT = Halofuginone lactate tablets

HS = Halofuginone lactate solution

* = One animal died of acute ECF on day 2

not been reached, the dramatic antischizont effect of halofuginone lactate could be manipulated to save valuable cattle. The use of furosemide (when clear signs of damage of macroschizonts are seen), for enhanced diuresis or saluresis and streptomycin sulphate to prevent secondary pulmonary infection are recom-

mended in the chemotherapy of ECF as supportive measures. And, a close eye on possible concurrent haemotropic diseases (anaplasmosis, babesiosis and trypanosomiasis) and their immediate control with appropriate drugs, will certainly raise the overall efficacy of halofuginone lactate in the treatment of ECF.

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