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Autor: Schein, E. / Voigt, W.P.
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Chemotherapy of bovine theileriosis with Halofuginone*

Short communication

E. SCHEIN, W. P. VOIGT

Theileriosis is a haemopprotozoal infection caused by members of the genus *Theileria*. The most important species in cattle are *T. parva*, *T. lawrencei* and *T. annulata*. In all cases *Theileriae* are transmitted by ticks, and the occurrence of the vector ticks determines the geographical distribution of the diseases in tropical and subtropical areas. The disease is characterized by extremely high mortality approaching 100% in fully susceptible cattle exposed to a heavy challenge. In East Africa half a million cattle die from East Coast Fever (ECF) per annum (Grootenhuis, 1979). ECF is the most important killer disease of cattle in this area. At present no specific curative drug exists for practical use to treat clinical cases. Antimalarial drugs have some effect on the piroplasms in the blood, but do not effect the course of the clinical theileriosis (Neitz, 1956).

Chlortetracyclines and oxychlortetracyclines given throughout the incubation period and the period of the first clinical reaction reduce the degree of parasitaemia and curtail the severity of clinical symptoms during the febrile phase (Neitz, 1953). Tetracyclines have a chemoprophylactic effect, but their use for treatment of the clinical theileriosis is limited (Radley et al., 1975).

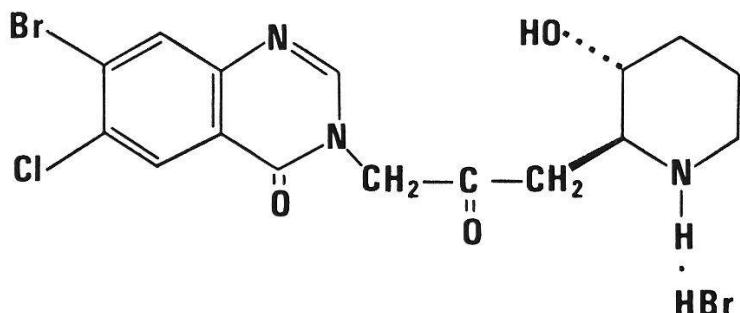
In the last years Menoctone [(Sterling-Winthrop) 2-hydroxy-3-(8-cyclohexyloctyl)-1,4-naphthoquinone] was shown to have an effect against theileriosis (Dolan and McHardy, 1976). In experimental *T. parva* infections and in in vitro studies it has been proved, that Menoctone had a potential anti-schizont activity (McHardy et al., 1976; McHardy, 1978) and seemed to be adequate for producing immunity.

The anti-coccidal substance Halofuginone seemed to be suitable for treatment-experiments in *Theileria* infections, because of its additional malaricidal and antipyretic action. The efficacy against poultry malaria is 100 times superior to that of Quinine.

* in memoriam W. O. Neitz

Correspondence: Prof. Dr. E. Schein, Institut für Parasitologie und Tropenveterinärmedizin, Königsweg 65, D-1000 Berlin 37

In this paper we report the first results of the treatment against theileriosis with Halofuginone [(Stenorol) (Roussel-Uclaf Paris/Hoechst AG) dl-trans-7-bromo-6-chloro-3-3' (3-hydroxy-2-piperidyl) acetonyl-4 (3H)-chinazolinon-hydrobromid (= $C_{16}H_{18}O_3N_3ClBr_2$)]:



During our experiments 12 young cattle (German Frisian) weighing between 95 and 180 kg were used. Six animals each were infected with the *T. annulata* strain Ankara (Experiment I) and with the *T. parva* strain Muguga (Experiment II), respectively. Stabilates or tick-attachment were used to infect the cattle. Prior to the application of the drug body temperature was measured and blood- and lymphnode smears were prepared daily. The same test-procedures were performed in a 6-h interval starting with the commencement of the application of Halofuginone. Four animals of each group were treated each with a total dose of 1.2 mg of Halofuginone per kg body weight. The therapeutic dose was administered per os either as a single dose or split over 2 or 4 days. Two animals of each group served as untreated controls. The therapy commenced when the infected animals showed clinical symptoms accompanied by body temperatures above 40° C and when the schizonts could be observed in lymph node biopsies. One infected animal was treated not earlier than on the sixth day of fever at a point of time at which the control animals were already closed to exitus. About four weeks after recovery all surviving cattle were challenged by attachment of 100 infected ticks.

Experiment I

Treatment of *T. annulata* infected cattle: All infected animals treated with Halofuginone survived. The body temperature decreased and was back to normal by 48 h post treatment (p.t.). The occurrence of degenerated schizonts with nuclear pycnosis was markedly suppressed in lymph node smears one day p.t. By the third to fourth day after treatment, no schizonts were found in the lymph node anymore. The first occurrence of piroplasms in the erythrocytes was recorded at day 8 p.t. A pertaining parasitaemia was of a very low level and did not exceed 1 parasite per 1000 erythrocytes (Fig. 1) during the time of observation. Both controls died at day 15 and 21 p.i., respectively. Four weeks p.t. the treated animals were exposed to a challenge by attaching individually 100

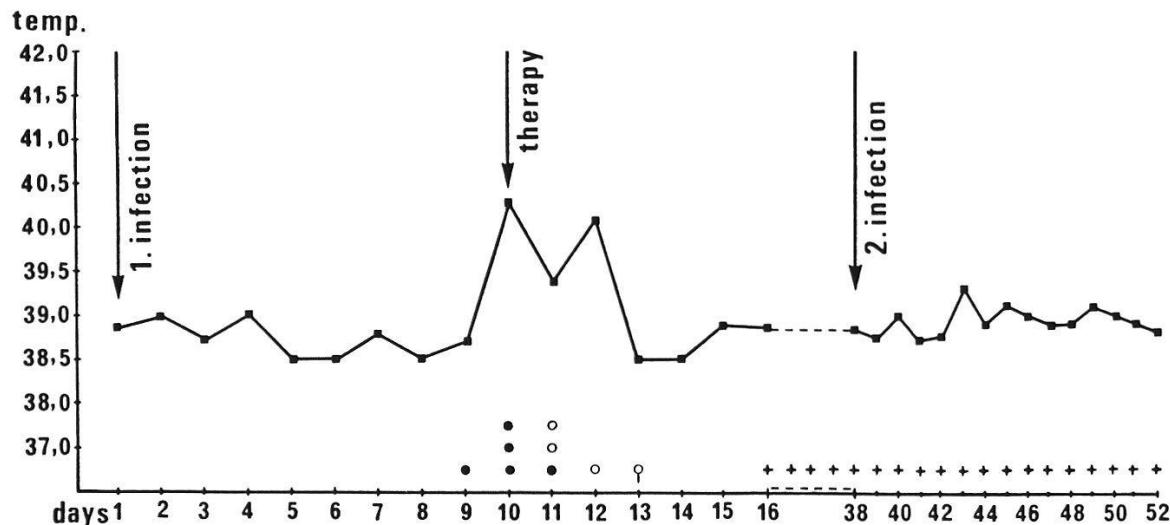


Fig. 1. Body temperature of *Theileria annulata* infected cattle before and after treatment with Halofuginone (1,2 mg/kg). ● = schizonts in lymph node; ○ = degenerated schizonts in lymph node; + = piroplasms in erythrocytes.

infected ticks (*Hyalomma a. excavatum*) to the ear. Except for mild swellings of the parotic lymph nodes, the treated animals did not produce clinical symptoms.

Experiment II

Treatment of *T. parva* infected cattle: All Halofuginone treated cattle survived and recovered, while the control animals died on day 16 and 20 p.i., respectively. In those three cattle having been treated at the onset of clinical disease body temperature returned to normal values and only a very few degenerated schizonts could be observed in the lymph node biopsies within 48 h after commencement of therapy. Within the erythrocytes no piroplasms could be found. The animal treated in very bad clinical condition not before a 6-day lasting fever period and showing ample numbers of Koch bodies in all lymph nodes returned to normal body temperature within 12 h after application of a single therapeutic dose. Another 12 h later many degenerated Koch bodies were visible in the lymph node biopsies; two days later no Koch bodies could be detected anymore. Piroplasms which occurred in this case already before the application of the drug could be observed during a period of 3 weeks p.i. in a very low number (Fig. 2). Four weeks p.t. all 4 animals were challenged individually by attachment of 100 infected ticks (*R. appendiculatus*) to the ears. In the animals a mild swelling of the parotic lymph node occurred but schizonts could not be demonstrated. There was no increase in body temperature.

During this preliminary study it could be shown, that Halofuginone is highly effective against theileriosis. The normally lethal experimental *T. parva* or *T. annulata* infections were treated successfully in bovine even during the

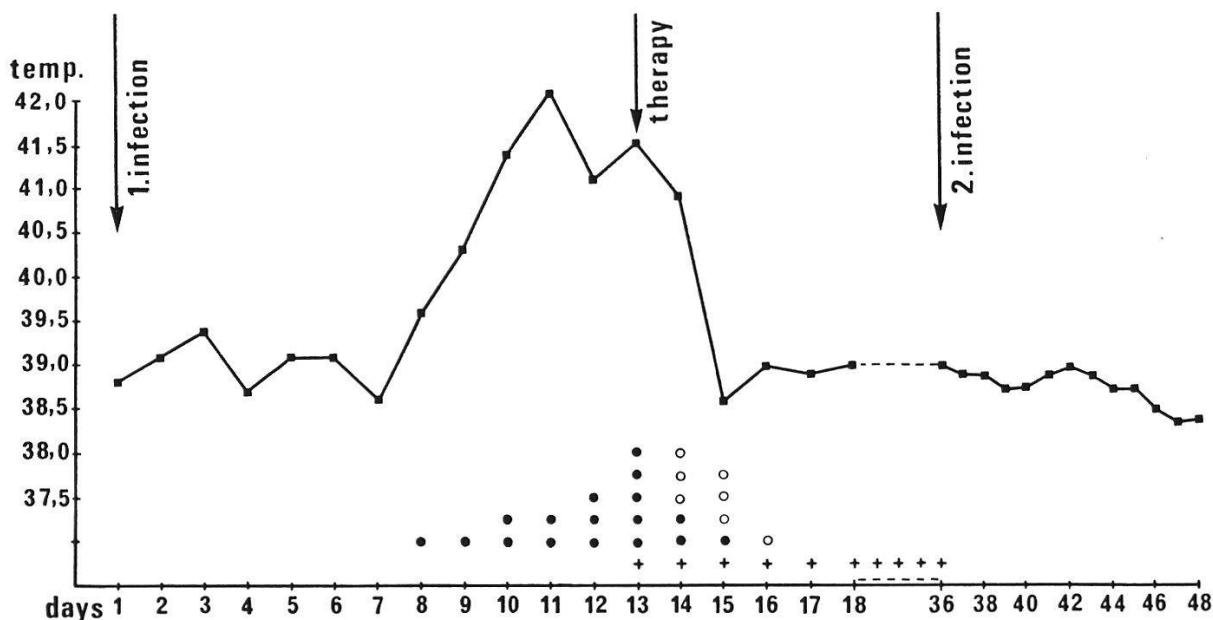


Fig. 2. Body temperature of *Theileria parva* infected cattle before and after treatment with Halofuginone (1.2 mg/kg). ● = schizonts in lymph node; ○ = degenerated schizonts in lymph node; + = piroplasms in erythrocytes.

advanced stage of the disease. Clinical symptoms disappeared within 24 h. Primarily, the action of the drug seems to be directed against the developmental stages of *Theileria* as shown by the degenerated schizonts. Further investigations have to reveal, whether sporozoites and piroplasms are affected as well. Until now, nothing is known about the mode of action of Halofuginone against *Theileria*.

All of the treated animals were immune against a high challenge infection with the same *Theileria* strain as used in the first infection. This finding provides some evidence that Halofuginone exerts not only a therapeutic effect but could be used for immunotherapeutical purposes as well.

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