

INHIBITION AND CONTROL OF TICK TRANSMITTED
ANAPLASMOSIS WITH ORALLY ADMINISTERED
TETRACYCLINES

By

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TETRACYCLINES

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TABLE OF CONTENTS

Chapter	Page
I. INTRODUCTION	1
Tetracyclines Used in the Treatment of Anaplasmosis . . .	2
Discussion of Research Problem.	3
II. THE BIOEQUIVALENCY OF OXYTETRACYCLINE AND CHLORTETRACYCLINE FOR CONTROL OF TICK TRANSMITTED ANAPLASMOSIS	5
Materials and Methods	5
Results and Discussion.	6
III. INHIBITION OF TICK TRANSMISSION OF ANAPLASMOSIS BY ORALLY ADMINISTERED CHLORTETRACYCLINE - TRAIL I	9
Materials and Methods	9
Results and Discussion.	12
IV. INHIBITION OF TICK TRANSMISSION OF ANAPLASMOSIS BY ORALLY ADMINISTERED CHLORTETRACYCLINE - TRIAL II.	15
Results and Discussion.	17
V. SUMMARY AND CONCLUSIONS	20
REFERENCES CITED.	22

LIST OF TABLES

Table		Page
I.	Bioequivalency of Oxytetracycline and Chlortetracycline for the Control of Tick-Transmitted Anaplasmosis	7
II.	Design of Drug Therapy and Injection of Gut Hemogenate to Determine Inhibition of Tick Transmission of Anaplasmosis.	11
III.	Influence of Chlortetracycline on the Transmission of Anaplasmosis by Ticks	13
IV.	Design of Drug Therapy, Injection of Gut Homogenate, and Transfer of Ticks to Determine Inhibition of Tick Transmission of Anaplasmosis	16
V.	Influence of Chlortetracycline on the Transmission of Anaplasmosis by Ticks	18

CHAPTER I

INTRODUCTION

Anaplasma marginale Theiler is a rickettsial infection of bovine erythrocytes. The disease is transmitted mechanically by the bites of horseflies (Tabanidae) and possibly other biting flies. Ticks are the only known biological vector of this disease and are probably responsible for its continuation (Dikmans 1950, Howell 1957). Factors that account for the efficiency of ticks as vectors of Anaplasmosis are (1) they attach firmly and do not dislodge easily; (2) they are slow feeding which permits efficient transfer of the pathogen; (3) their longevity increases the chance of acquiring and transmitting the disease; (4) they are relatively free from natural enemies; and (5) they are resistant to environmental stresses (Harwood and James 1979).

Of the ticks implicated as vectors of anaplasmosis Dermacentor variabilis (Say) and D. andersoni Stiles are the most important. Several authors have demonstrated the vector ability of experimentally and naturally infected ticks of these species and transtadial transmission of the pathogen (Anthony and Roby 1962, Kocan et al. 1980, Kocan et al. 1981, Boynton et al. 1936). Howell et al. (1941) demonstrated transovarial transmission by D. andersoni but subsequent research has failed to substantiate this. Transmission of the pathogen to the bovine host may be by the bite or by contamination of the tick feces.

A. marginale causes an acute, subacute, or chronic infectious

anemia of the bovine. The disease is usually mild in calves up to 1 year old and acute in older cattle (Ristic 1960). Survival of infected animals is increased if the disease is diagnosed and treated early before onset of complications resulting from the anemia. A vaccine is available for anaplasmosis but treatment with tetracyclines remains important in the control of the disease.

Tetracyclines Used in the Treatment and Control of Anaplasmosis

The only chemotherapeutic compounds available for use against anaplasmosis in the United States are oxytetracycline, chlortetracycline, and tetracycline hydrochloride. They are approved for intramuscular (IM) and intravenous (IV) injection and oral administration. They show similar activity in inhibiting reproduction by A. marginale (Simpson 1975, Brock 1959).

Treatment of anaplasmosis is most commonly affected by IM or IV administration of one of the tetracyclines. Foote et al. (1951) were the first to note the effectiveness of IV administered chlortetracycline against anaplasmosis. Miller et al. (1953) reported slightly better success in treating anaplasmosis with chlortetracycline IV than with oxytetracycline IV especially when the disease was treated early in its course. Foote and Wulf (1952) reported that doses of 27.5 to 47.5 grams of chlortetracycline administered over 3 days eliminated the infection from bovine erythrocytes. This was refuted by Pearson and Brock (1953) who reported that dosages of 47.5 g only temporarily suppressed the infection and did not eliminate it. Several authors have reported success in eliminating the carrier state by treating the animal with

high levels of tetracyclines for 5 to 10 days or the use of a long acting oxytetracycline (Pearson et al. 1957, Magonigle et al. 1975, Robey et al. 1978). Other authors demonstrated that acute cases of anaplasmosis can be successfully treated with 3 treatments of oxytetracycline formulated at 50 mg/ml or 1 treatment of a long-acting oxytetracycline formulated at 200 mg/ml (Kuttler 1971, Kuttler and Simpson 1978, Wilson et al. 1979).

Feeding chlortetracycline is an accepted method for the prevention of anaplasmosis and the elimination of the carrier state. Several authors have reported successfully preventing anaplasmosis or eliminating the carrier state by feeding chlortetracycline to animals on drylot at a dosage of 1.1 mg/kg body weight for periods of 60 to 120 days (Brock et al. 1957, Franklin et al. 1967, Richey et al. 1977). Similar studies were conducted on pastured animals and reductions in the number of carrier animals were reported but the reduction was accomplished over longer periods of time than in animals kept on drylot. This reduction in efficiency may be due to the poor palatability of the medicated feeds or to the variable consumption of the medicated feeds.

Discussion of Research Problem

Anaplasmosis is spreading in the United States. McCallom (1976) estimated that at that time 50,000 to 100,000 animals died of the disease. Losses were estimated to exceed 100 million dollars a year from these deaths and abortions caused by lack of oxygen to the fetus. A vaccine is available but it does not eliminate the carrier state of the disease. Treatment using the tetracyclines remains an important method of limiting the losses caused by anaplasmosis. Early diagnosis

is difficult because the disease can remain undetected by the producer until the animal is too sick to be treated without risk (Koger 1962, Kuttler 1973).

Recent research at Oklahoma State University has been aimed at making treatment and prophylaxis of the disease more cost effective and less detrimental to the animal by using sustained-release boluses (Byford 1980, 1981). To accomplish this it was important to determine if oxytetracycline or chlortetracycline is more efficient for control of the disease; and to determine if a tetracycline could prevent infected ticks from transmitting A. marginale to uninfected cattle.

CHAPTER II

THE BIOEQUIVALENCY OF OXYTETRACYCLINE AND CHLORTETRACYCLINE FOR CONTROL OF TICK TRANSMITTED ANAPLASMOSIS

Previous researchers have reported that low level treatment with tetracyclines administered orally or by injection for extended periods of time can control bovine anaplasmosis (Pearson et al. 1957, Byford et al. 1981). Recent research at Oklahoma State University has indicated that such dosages could be administered via a sustained-release bolus (Byford et al. 1981). To further the efficiency of this administration system and others using orally administered tetracyclines, it was determined that a bioequivalency study was necessary. The purpose of this study was to determine if oxytetracycline or chlortetracycline is more efficient for the control of tick transmitted anaplasmosis.

Materials and Methods

Test animals consisted of seven Holstein and Jersey dairy cows that were 4-6 years of age. Wright-stained blood smears and the anaplasmosis complement-fixation test were used to determine if the test animals had any previous exposure to anaplasmosis.

The cattle were randomly divided into 2 test groups of 3 animals each and 1 animal served as a control. All test animals were maintained under drylot conditions on a cottonseed hull based ration and wheat

straw free-choice to minimize weight gain. Group I received oxytetracycline at a dosage rate of 1.1 mg/kg body weight. Group II received chlortetracycline at a dosage rate of 1.1 mg/kg body weight. Both drugs were administered orally using gelatin capsules containing the drug and barium sulfate to increase the density of the capsule. Drug dosages for each animal were determined from weekly weight measurements. Administration of the drugs began on test day 0 and continued for 120 days.

Anaplasmosis infective D. variabilis were obtained by feeding the nymphal ticks on a cow inoculated with A. marginale that developed a peak parasitemia of 35.6 percent. All ticks for this study were fed on one infected cow to minimize differences in infectivity of ticks. These ticks were allowed to molt to the adult stage for use in this study.

On day 10 of the study all test animals were placed in stanchions and exposed to A. marginale by feeding the infective adult ticks on the susceptible animals. The animals were subsequently monitored 3 times each week until the appearance of marginal bodies and daily thereafter to determine the bioequivalency of the drugs. Packed cell volumes, the anaplasmosis complement fixation tests, and parasitemia values were measured at each sampling to determine the efficacy of each drug therapy. Monitoring of the animals continued for 120 days.

Results and Discussion

Transmission of anaplasmosis by infected ticks was achieved in those animals receiving oxytetracycline and in the control animal. The influence of each treatment is shown in Table I. The control animal developed a severe case of anaplasmosis as is evident from the minimum PCV of 10.5 percent and the loss of 86.4 kgs from the mean preinfection

TABLE I
BIOEQUIVALENCY OF OXYTETRACYCLINE AND CHLORTETRACYCLINE
FOR THE CONTROL OF TICK^a TRANSMITTED ANAPLASMOSIS

Treatment	Cow Number	Prepatent ^b Period (days)	Packed Cell Volume ^c		Peak Parasitemia Percent
			Mean Preinfection	Minimum Percent	
Oxytetracycline	509	27	34.0	20.5	1.6 ^d
Oxytetracycline	528	43	33.5	23.0	0.8 ^d
Oxytetracycline	3067	28	31.5	25.5	0.6 ^d
Chlortetracycline	322				0.0
Chlortetracycline	3068				0.0
Chlortetracycline	3178				
Control	448	27	33.0	10.5	13.2 ^d

^a All ticks infected on cow number 203.

^b Prepatent period determined from day 5 post attachment to appearance of marginal bodies in stained blood smears.

^c Packed cell volumes reported for animals showing an infection of A. marginale.

^d Positive reaction to CF titer at 1:5 dilution of serum

weight even though the peak parasitemia was 13.2 percent. The animals receiving 1.1 mg/kg body weight of oxytetracycline developed mild cases of anaplasmosis as evidenced by the peak parasitemia of the animals (1.6, 0.8 and 0.6 percent). The animals receiving 1.1 mg/kg body weight of chlortetracycline showed no signs of anaplasmosis in the stained blood smears or in the complement fixation test.

Treatment with oxytetracycline showed some effectiveness in limiting the infection in those animals receiving it. It was also effective in preventing expression of clinical signs of the disease. Treatment with chlortetracycline was completely effective in preventing infection in those animals receiving it. Based on the results of these treatments chlortetracycline proved to be more efficient for the control of anaplasmosis than oxytetracycline.

CHAPTER III

INHIBITION OF TICK TRANSMISSION OF ANAPLASMOSIS

BY ORALLY ADMINISTERED CHLORTETRACYCLINE -

TRAIL I

Tetracyclines are the only chemotherapeutic compounds available for use against anaplasmosis in the United States. No research has been conducted concerning the ability of these compounds to inhibit the transmission of anaplasmosis by ticks. Because of their common use in the control and treatment of the disease this aspect of the transmission cycle was considered important. If the tetracyclines could inhibit the transmission of the disease, the disease cycle could be broken at two points; the bovine host and the tick vector of the disease. The purpose of this study was to determine if infected adult ticks could be prevented from transmitting anaplasmosis to uninfected cattle.

Materials and Methods

Test animals for the first part of this study consisted of 4 Holstein dairy cows that were 4-6 years of age. Wright-stained blood smears and the complement-fixation test were conducted to determine if these animals had any previous exposure to anaplasmosis.

All ticks used in this study were infected as nymphs with A. marginale by placing them on a calf inoculated with this disease. To minimize possible differences in infectivity, nymphal D. variabilis

were fed on one calf. They were subsequently allowed to molt to the adult stage for use in this study.

The 4-6 year old dairy cows were assigned a treatment regiment as shown in Table II. One cow was not treated with chlortetracycline and served as a control. The remaining 3 cows received chlortetracycline at dosage rates of 1.0, 2.0 and 3.0 mg/kg body weight. The treatments were administered orally using gelatin capsules containing the drug and barium sulfate to increase the density of the capsule to prevent regurgitation. Drug dosages for each animal were determined from weekly weight measurements. Administration of the drug began on test day 0 and continued for 120 days. On day 10 of the study the cows were placed in stanchions and exposed to 100 pair of infected female D. variabilis. They were subsequently monitored 3 times each week until the appearance of marginal bodies in a stained blood smear and daily thereafter. Packed cell volumes and the anaplasmosis complement-fixation test were used in addition to the stained blood smear to monitor the progress of the disease.

Splenectomized calves were used to indicate the effect of the drug treatment given to the dairy cows on the infectivity of the ticks. Gut homogenate was prepared from a pool of 50 of the infected ticks removed from a cow on day 16 of the test. The gut homogenate from the appropriate cow was injected into a splenectomized calf according to Table II. The calves were monitored 3 times each week until marginal bodies appeared in the stained blood smear and daily thereafter. Packed cell volumes and the anaplasmosis complement-fixation test were used to aid in monitoring the progress of the disease.

TABLE II
DESIGN OF DRUG THERAPY AND INJECTION OF GUT
HOMOGENATE TO DETERMINE INHIBITION OF
TICK TRANSMISSION OF ANAPLASMOSIS

Chlortetracycline Dosage	Cow ^a Number	Gut Homogenate ^b from Cow Injected into Calf Number
Control	3068	J1
1.0 mg/kg	3125	J2
2.0 mg/kg	3178	J3
3.0 mg/kg	3131	J4

^a All cows were infested with 100 adult D. variabilis on day 10 of study.

^b Gut homogenate from a pool of 50 ticks.

Results and Discussion

The 4-7 year old dairy cows did not develop an A. marginale infection as was shown by negative CF titers and the absence of marginal bodies in the stained blood smears for the monitoring period of 120 days. The ticks were found to be infective when gut homogenates prepared from them caused an infection in the splenectomized calves used in this study. Therefore why the dairy cows remained uninfected could not be explained.

All calves injected with the gut homogenate did develop A. marginale infections. Results of this part of the study are presented in Table III. The prepatent period for all calves was in the normal range and showed no significant pattern in relation to the level of chlortetracycline administered. Peak parasitemia also showed no pattern in relation to the level of chlortetracycline administered. The data indicate that chlortetracycline administered at these rates had no effect on the ability of ticks to transmit A. marginale between bovine hosts. This may be due to the dosage level administered to the cow was insufficient to maintain the blood concentration at a level that would reduce the infectivity of the tick. It is also possible that sufficient levels were not maintained within the tick for a long enough period to reduce the infectivity of the tick due to the limited time in which feeding actually occurred. Feeding trials involving the bovine host have demonstrated success in eliminating the carrier state with low levels of tetracyclines but only if the drug was administered for 60 to 120 days. Recent studies by Kocan et al. (1980) demonstrated that the development sites of A. marginale in the tick vector is within the gut epithelial

TABLE III
INFLUENCE OF CHLORTETRACYCLINE ON THE TRANSMISSION
OF ANAPLASMOSIS BY TICKS

Chlortetracycline Dosage Administered Cow	Calf Number	Prepatent ^a Period (days)	Packed Cell Volume		Peak Parasitemia Percent
			Mean Preinfection	Minimum Percent	
Control	J1	29	33.5	10.0	15.6 ^b
1.0 mg/kg	J2	26	33.0	12.5	33.8 ^b
2.0 mg/kg	J3	28	31.0	17.0	13.1 ^b
3.0 mg/kg	J4	31	39.5	11.5	26.9 ^b

^a Prepatent period determined from day of injection of gut homogenate to appearance of marginal bodies in the stained blood smears.

^b Positive reaction to CF titers at 1:5 dilution of serum.

cells. It is possible that chlortetracycline did not penetrate the gut epithelium in sufficient concentration to reduce the infectivity of the tick.

The results of this study indicated that chlortetracycline administered orally to the bovine host had no effect on the ability of ticks to transmit A. marginale. The reason for this was not known and further studies were conducted to study this problem further.

CHAPTER IV

INHIBITION OF TICK TRANSMISSION OF ANAPLASMOSIS

BY ORALLY ADMINISTERED CHLORTETRACYCLINE-

TRIAL II

After the completion of Trial I, it was determined that the use of gut homogenates prepared from ticks parasitizing chlortetracycline treated cattle, was insufficient to test the effect of the treatment on the tick's infectivity. Also the anomalous results obtained from the dairy cows contributed to the need for a second study to eliminate the possibility of contamination of the gut homogenate and to simulate a field situation. Transfer of live whole ticks to susceptible splenectomized dairy calves were used as a further indicator of the effect of the treatment regiment.

Test animals for this study were 2 Ayrshire dairy cows, 4-7 years of age and 6 splenectomized Holstein dairy calves. The cattle were treated as shown in Table IV. One dairy cow served as an untreated control and chlortetracycline was administered to the other dairy cow at a dosage rate of 3 mg/kg body weight in 2 daily doses until day 72 in the same manner as before. After exposure to 100 pair of infected D. andersoni on day 10 hematologic and serologic tests previously described were used to monitor the progress of the disease. The splenectomized calves were treated as shown in Table IV. After administration of the appropriate treatment to the splenectomized calves

TABLE IV
DESIGN OF DRUG THERAPY, INJECTION OF GUT HOMOGENATE,
AND TRANSFER OF TICKS TO DETERMINE INHIBITION
OF TICK TRANSMISSION OF ANAPLASMOSIS

Chlortetracycline Dosage	Cow Number	Cut Homogenate from Cow Injected into Calf Number	Tick transferred from Cow onto Calf Number
Control	710	384	388
		406	
3 mg/kg	3042	404	386
		405	

hematologic and serologic tests were conducted as previously described to monitor the progress of the disease in the calves.

Results and Discussion

The 4-7 year old dairy cows developed an A. marginale infection as shown in Table V. The prepatent period was in the normal range for cattle infected by tick vectors. It should be noted that the prepatent period of the cow treated with chlortetracycline is not definite because the complement fixation test for anaplasmosis remained negative. The peak parasitemia of the cow treated with chlortetracycline did not reach a level sufficient to cause clinical symptoms or a significant decrease in the packed cell volume. The minimum packed cell volume noted in Table V did not follow the peak parasitemia as is common in anaplasmosis and therefore was not due to the disease. The data indicate that 3 mg/kg body weight of chlortetracycline is sufficient to prevent expression of clinical symptoms of anaplasmosis.

All calves injected with gut hemogenate or parasitized by the 25 pair of ticks developed an A. marginale infection. These results are presented in Table V. As was noted in the initial study the prepatent period was within the normal 20-25 day prepatent period expected and showed no pattern in relation to the treatment received by the dairy cow the ticks were initially fed on. Peak parasitemia also showed no significant pattern in relation to the treatment received by the dairy cow. The data indicate that chlortetracycline did not have an effect on the ability of ticks to transmit A. marginale between bovine hosts as in the initial study. This study further indicated that injection of gut hemogenates accurately reflected the ability of the tick to

TABLE V
INFLUENCE OF CHLORTETRACYCLINE ON THE TRANSMISSION
OF ANAPLASMOSIS BY TICKS^a

<u>CALVES</u>			(%)		
Number	Cow Ticks from	Prepatent Period	Peak Para- sitemia	Init \bar{X} PCV	Low PCV
384	710	17 ^{a,b}	51.2	33.5	10.0
386	3042	24 ^c	48.2	33.6	10.0 [*]
388	710	25 ^c	34.0	32.2	8.5 [*]
404	3042	22 ^b	34.2	30.4	10.0
405	3042	21 ^b	41.6	34.2	10.0
406	710	20 ^b	41.2	39.2	8.5
<u>COWS</u>					
710		23 ^c	23.2	31.5	9.5 [*]
3042		30 ^d	0.2	41.5	35.0

^a All ticks infected on calf number 378.

^b Prepatent period determined from day of injection of gut hemogenate to appearance of marginal bodies in the stained blood smears.

^c Prepatent period determined from day 5 post attachment to appearance to marginal bodies in stained blood smears.

^d Prepatent period determined from day 6 post attachment to suspected appearance of marginal bodies in stained blood smears.

transmit A. marginale after feeding on antibiotic treated cattle. This finding agrees with research conducted by Kocan et al. (1980) which demonstrated that the development site of A. marginale in the tick is within the gut epithelia.

Trial I and this study indicated that orally administered chlortetracycline cannot destroy or reduce the infectivity of ticks parasitizing a treated cow. Increasing the dosage rate administered to the host animal might prove to be effective in reducing the infectivity of ticks but would probably be prohibitively expensive. Also increased dosage rates would not be practical with present sustained release systems. Adding sufficient quantities to feed would probably not be feasible because of the reduction in the feeds palatability which would reduce the actual dose received by the animal. In summary chlortetracycline does not show an ability to reduce the efficiency of tick transmission of anaplasmosis.

CHAPTER V

SUMMARY AND CONCLUSIONS

The objective of these studies was to evaluate the efficacy of oxytetracycline and chlortetracycline for the prevention of anaplasmosis and to determine if chlortetracycline would inhibit the transmission of anaplasmosis by ticks. These factors were determined to be important to aid in the development of the most practical and efficient sustained-release bolus to be used for control and prevention of anaplasmosis.

Data from the bioequivalency study indicated that chlortetracycline was more efficient than oxytetracycline for the control of tick born anaplasmosis, when the drugs were administered orally. The oxytetracycline treated animals developed mild infections, therefore demonstrating oxytetracycline's benefits whereas the chlortetracycline treated animals remained free of infection.

Data from the study on chlortetracycline's ability to inhibit anaplasmosis transmission, indicated that ticks remain infective after feeding on chlortetracycline treated animals. This was demonstrated by the successful transmission of the disease to susceptible calves by gut homogenates and transfer of ticks that were parasitizing treated cattle. This study indicated that the transmission cycle of A. marginale could not be effectively interrupted in the tick by the use of chlortetracycline.

The tetracyclines have been important in the control of anaplasmosis

but current methods of treatment are laborious. When tetracyclines are added to feeds their effectiveness against anaplasmosis is variable due to the reduced palatability of the feed. The oxytetracycline sustained-release bolus reported on by Byford et al. (1981) was shown to be effective against anaplasmosis and could solve these problems. The results of these studies indicate that the efficiency of this system could be increased by using chlortetracycline as the active ingredient instead of oxytetracycline.

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