Preliminary efficacy trial of Cymelarsan in dogs and mice artificially infected with *Trypanosoma brucei* isolated from dogs in Nigeria

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Key words

Dog - Mouse - *Trypanosoma brucei* - Cymelarsan - Trypanocide - Experimental infection - Nigeria.

Summary

Efficacy of Mel Cy (Cymelarsan, Rhône Mérieux, France) against *Trypanosoma brucei* isolated from dogs was studied in experimentally infected mice and dogs. The mice were infected with parasites collected from five dogs and treated once intraperitoneally with Mel Cy at dose rates of 2.5 and 5.0 mg/kg seven and 14 days after infection, to give an indication on parasite sensitivity. Relapse of the parasitemia occurred in all groups of mice treated 14 days after infection, while almost all the mice treated seven days after infection remained parasitologically negative during the 63-day observation period. Five dogs were infected with a stock of the parasite then treated on the following postinfection days: day 7 (one dog), day 14 (two dogs), and day 21 (two dogs), at a dose of 2.5 mg/kg subcutaneously and on two consecutive days. Following the Mel Cy treatment, improvements in the clinical condition as well as weight gains were recorded in the dogs. A relapse of the infection occurred in only one of the two dogs treated 14 days after infection. Neither the dog treated at day 7 nor those treated at day 21 postinfection relapsed. It thus appears that, at the dose regimen used in this study, Mel Cy might be effective in the treatment of trypanosomosis due to *T. brucei* in dogs.

■ INTRODUCTION

Trypanosoma brucei infection in dogs is common in the Southeastern part of Nigeria (1, 14) and deadly for them (2, 12, 20). The commonly used drug for chemotherapy is diminazene aceturate at 7 mg/kg body weight but sometimes isometamidium chloride is used at 0.5-1 mg/kg (9, 24, 25). Treatment of the disease with these trypanocides is believed to have a variable success (2, 3, 4, 9, 20). While treatment failures have been associated with parasites which invade the brain, thus escaping the action of drugs which do not cross the blood brain barriers (8, 12), low efficacy of drugs to the emergence of trypanosomal resistance is another serious problem plaguing chemotherapy of trypanosomosis (6), and highlighting the need for new trypanocidal drugs.

Melarsenoxide cysteamine (Mel Cy, Cymelarsan, Rhône Mérieux, France) is a trivalent arsenical compound recently developed for treatment of infections with trypanosomes of the *brucei* group (19). It is related to the drug Arsobal which together with the newly introduced difluoromethylornithine (DFMO) are the only treatments available for the late stage of sleeping sickness in humans (11). Mel Cy has been shown to be effective against *T. evansi* infection in camels and cattle at dose rates between 0.625 and 1.25 mg/kg (18, 24). Furthermore, it has been shown to be effective against *T. evansi* stocks resistant to quinapyramine and suramin and *T. brucei* stocks resistant to diminazene aceturate (17, 26).

This study was undertaken to determine the effect of Mel Cy against *T. brucei* stocks isolated from dogs in Nsukka area, Nigeria, in the mouse and the dog, the definitive host.

■ MATERIALS AND METHODS

Experimental animals

Dogs

Five young local dogs (3 males and 2 females) weighing between 5.5 and 6.5 kg were used for the study. They were kept in fly-proof housing, fed once daily, and water was provided *ad libitum*. Prior to the study, a conditioning period of two weeks was allowed during which time the dogs were dewormed with ivermectin (Ivomec Merck Sharp and Dohme B.V. Haarlem, Holland) at a dosage of 0.2 mg/kg subcutaneously (s.c.) and confirmed parasitologically negative for trypanosomes by wet blood film, Giemsa-stained thin blood smears and the hematocrit buffy coat method (13) .

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Mice

A total of 65 white albino mice of both sexes were used. They were kept in clean cages in a fly-proof house and were fed and watered *ad libitum*.

Trypanosome infections

Trypanosoma brucei stocks isolated from clinically infected dogs were used in the study. The trypanosomes were identified morphologically on Giemsa-stained thin film preparations (22). Both the dogs and mice were infected intraperitoneally (i.p.) with 5 x 10^5 trypanosomes per milliliter of saline diluted infected blood. The number of parasites was assessed by the method of Herbert and Lumsden (5).

Experimental design

Dogs

After infection, the onset of parasitemia was determined by a daily examination of wet blood film, Giemsa-stained thin blood smears and the hematocrit buffy coat method (13) and subsequently treated in three categories as indicated in table I: one dog (No. 1) was treated after one week, two dogs (Nos. 2 and 3) after two weeks and the two remaining dogs (Nos. 4 and 5) after three weeks of infection with Mel Cy at the dosage of 2.5 mg/kg s.c. daily for two days. Parasite clearance time was established by blood examination at ten minutes' intervals posttreatment. The dogs were monitored for parasitemia (i.e., relapses) every seventh day for 63 days posttreatment.

All the dogs were closely observed throughout the study period for clinical signs. Daily rectal temperatures were recorded and packed cell volume (PCV) and body weights determined weekly for use in the assessment of the drug therapeutic efficacy. Pre-infection parameters were obtained one week before and on the day of infection.

Mice

A total of five *T. brucei* stocks isolated from different dogs were used to infect five groups of mice, respectively, then treated with Mel Cy as shown in table II. The drug was administered i.p. as a single dose immediately after reconstitution and appropriate dilution in distilled water to achieve the desired dosage.

Onset of parasitemia, parasite clearance time and parasitemia were also determined as above using tail blood.

■ RESULTS

Dogs

Clinical findings

Disease symptoms were apparent only in dogs infected two to three weeks before treatment and included depression, apathy, anorexia, ocular discharge, enlargement of lymph nodes, dullness, anemia, pyrexia ranging from 39 to 40.5°C and edema of the face.

The drug appeared to be well tolerated by the dogs as no untoward effects were noticed following administration.

Parasitemia

The dogs were trypanosome positive by 5 to 7 days after inoculation and the parasitemia persisted until treatment one to three weeks after infection (table I). Trypanosomes disappeared from the dogs' blood within 30 min of Mel Cy treatment, followed by the remission of the infection clinical signs. Relapse of parasitemia did not occur in the dogs except in dog No. 2 , where it was detected on day 49 after treatment (day 63 after infection).

Packed cell volume, body weight and temperature

PCV values are shown in table III. Infection was associated with a decrease in PCV, which was apparent from the second week after infection, but was reversed following treatment. The relapse infection recorded in dog No. 2 (day 63 after infection) also caused a fall in PCV.

Periods of infection and relapse infection were characterized by negative weight gains, while progressive weight gains accompanied Mel Cy treatment (table IV).

Average weekly temperature of the dogs is shown in table V. Both the initial infection and posttreatment relapse (dog No. 2) caused elevation of body temperatures.

Mice

The prepatent period of infection for isolated *T. brucei* stocks was 4 to 6 days and parasitemia was thereafter sustained in the absence of treatment (controls) until death. The infected mice response to treatment with varying levels of Mel Cy is shown in table II. Irrespective of doses administered, parasites were cleared from the blood of infected mice within 30 min of treatment in mice treated seven days after infection, whereas clearance was achieved in

Table I

Parasitemia of dogs infected with *Trypanosoma brucei* and treated with Cymelarsan

Dogs	Days after infection													
	-7	0	7	14	21	28	35	42	49	56	63	70	77	84
1	-	-	+*	-	-	-	-	-	-	-	-	-		
2	-	-	+	+*	-	-	-	-	-	-	+			
3	-	-	+	+*	-	-	-	-	-	-	-	-	-	
4	-	-	+	+	+*	-	-	-	-	-	-	-	-	-
5	-	-	+	+	+*	-	-	-	-	-	-	-	-	-

+: Parasitemia
-: Aparasitemia
* Treatment with Cymelarsan
-7: One week before infection
0: Day of infection

Table II

Response of *Trypanosoma brucei*-infected mice to treatment with different levels of Cymelarsan

Isolate	Dosage (mg/kg)	Duration of infection before treatment (days)	Period of monitoring (weeks)									
			0*	1	2	3	4	5	6	7	8	9
I	2.5	7	3/3**	0/3	0/3	0/2	0/2	0/2	0/2	1/2	1/2	1/2
	5.0	7	3/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	25.0	7	3/3	0/2	0/2	0/2	0/2	0/2	1/2	1/2	1/2	1/2
	50.0	7	3/3	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2.5	14	3/3	0/3	0/3	3/3	3/3					
	5.0	14	3/3	0/2	0/2	2/2						
	Control		2/2	2/2	2/2	1/1	0/0					
II	2.5	7	3/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	5.0	7	3/3	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
	2.5	14	3/3	0/3	2/3	2/3	3/3					
	5.0	14	3/3	0/3	2/3	2/3	2/3	2/3	2/3	2/3	2/3	2/3
	Control		2/2	2/2	2/2	1/1	0/0					
III	2.5	7	3/3	0/3	0/2	0/2	0/1	0/1	0/1	0/1	0/1	0/1
	5.0	7	3/3	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
	2.5	14	3/3	0/3	1/3	1/1	1/1	1/1	1/1	1/1	1/1	1/1
	5.0	14	3/3	0/3	0/3	2/3	2/3	3/3				
	Control		3/3	3/3	2/2	1/1	0/0					
IV	2.5	7	3/3	0/3	0/3	0/3						
	5.0	7	3/3	0/2	0/2	0/2						
	Control		2/2	2/2	2/2	2/2	2/2	1/1	1/1	1/1	1/1	1/1
V	2.5	14	3/3	0/2	0/2	1/2	2/2	2/2	2/2			
	5.0	14	3/3	0/3	0/3	0/2	1/2	1/2	1/2			
	Control		2/2	2/2	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1

* Day of treatment
** Numerator = The number of mice that relapsed in the treated group
Denominator = The number of mice treated in the group

Table III

Packed cell volume of dogs infected with *Trypanosoma brucei* and treated with Cymelarsan

Dogs	Days after infection													
	-7	0	7	14	21	28	35	42	49	56	63	70	77	84
1	31	31	33*	24	31	31	38	25	31	40	33	38	-	-
2	33	34	35	26*	20	26	35	30	26	36	25	-	-	-
3	32	37	30	28*	34	36	38	36	39	36	40	38	42	-
4	34	32	30	23	28*	32	32	30	36	39	36	46	40	43
5	25	26	29	26	16*	31	38	34	37	39	38	40	34	37

* Treatment with Cymelarsan

Table IV

Weights (kg) of dogs infected with *Trypanosoma brucei* and treated with Cymelarsan

Dogs	Days after infection													
	-7	0	7	14	21	28	35	42	49	56	63	70	77	84
1	6.5	6.5	6.3*	7.5	7.5	7.5	8.0	8.5	9.0	9.0	10.0	10.0	-	-
2	6.5	6.5	6.5	7.0*	6.0	7.0	7.0	8.0	8.0	8.0	7.5	-	-	-
3	6.5	7.0	7.0	7.0*	6.5	7.0	7.5	8.5	8.5	9.0	9.0	9.5	10.0	-
4	6.0	6.0	7.0	7.0	7.0*	7.0	7.0	7.5	8.0	8.5	8.5	8.5	9.0	9.0
5	5.5	5.5	6.5	6.0	6.0*	6.5	7.0	7.5	8.0	9.5	10.0	10.0	10.5	10.5

* Treatment with Cymelarsan

Table V

Average weekly temperature (°C) of dogs infected with *Trypanosoma brucei* and treated with Cymelarsan

Dogs	Days after infection													
	-7	0	7	14	21	28	35	42	49	56	63	70	77	84
1	39.0	39.2	39.7*	39.3	38.7	38.3	38.3	38.2	38.3	38.5	38.3	38.2	-	-
2	38.6	38.5	39.5	39.8*	39	38.6	38.6	38.7	38.4	38.6	39.2	-	-	-
3	38.9	38.5	39.0	40.0*	38.6	38.2	38.4	38.5	38.8	39	38.5	38.6	38.4	-
4	38.5	38.6	39.0	39.6	38.2*	38.3	38.6	38.3	38	38.2	38.2	38.4	38.5	38.1
5	38.6	38.4	39.0	39.2	38.5*	38.2	38.4	38.3	38.2	38.8	39.4	38.9	38.7	38.6

* Treatment with Cymelarsan

40 to 60 min in mice treated 14 days after infection. Relapse occurred in all trypanosome stocks when treatment was administered 14 days postinfection, whereas, apart from trypanosome isolate No. 1, no relapses occurred when treatment was administered 7 days posttreatment within the study period.

■ DISCUSSION

Complete clearance of *T. brucei* from the blood of dogs within 30-60 min after treatment with Mel Cy coupled with improvement in the other parameters (temperature, PCV and body weight) have confirmed that the drug was effective within the dosage used. It further showed that the drug acted very fast compared to other trypanocides used in the treatment of trypanosomosis in dogs such as diminazene aceturate and isometamidium chloride with parasite clearance time of 24-48 hours (3, 15). Other authors also showed the rapid trypanocidal activity of the drug (trypanocides were destroyed within a few hours) (18, 27). The relapse in dog No. 2 treated two weeks after infection might be associated with some intrinsic factors of that particular dog (6, 16). This is in view of the fact that no relapses occurred in any of the two dogs treated three weeks after infection. An inverse relationship has been established between the duration of infection and the occurrence of relapse (i.e., the longer the infection lingered before treatment, the earlier the relapse) (7, 8). The absence of relapse in the dogs treated after three weeks of infection suggests that Mel Cy might be effective in the treatment of late stage canine *T. brucei* infection. However, results in mice would seem to be contradictory, although only one treatment was applied unlike in the dogs where two consecutive doses were administered. Furthermore, it has been noted that

mouse-sensitivity tests should only serve as a guide to the parasite sensitivity and not be used to predict curative doses for large animals (21).

The clinical signs exhibited by the infected dogs were typical of trypanosomosis (2, 10, 15). All dogs had rather low PCVs before infection (25) and this could not be associated with poor nutrition or internal parasitism since the dogs were treated for internal parasites before the study started and the feeding was considered adequate. The Mel Cy dose used appeared to be below the toxic or lethal dose for dogs as no clinically noticeable adverse effects were detectable. The dosage increase from 0.25mg/kg recommended for camels to 2.5 mg/kg in the dogs arose out of previous observations where lower doses were ineffective (P. Jeffries, pers. communic.). Even though no signs of toxicity were seen in the treated five dogs, a more extensive toxicity study in dogs is needed. Higher treatment levels were achieved in cattle when the drug was administered intramuscularly (i.m.) as opposed to subcutaneously (17, 18) because of the greater bioavailability of the drug when administered i.m.. However, i.m. injection of Mel Cy in dogs caused severe swelling at the site of injection which interfered with movement (unpublished data).

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Résumé

Anene B.M., Ogbuanya C.E., Mbah E.S., Ezeokonkwo R.C. Essais préliminaires pour tester l'efficacité de Cymelarsan chez des chiens et des souris infectés artificiellement par *Trypanosoma brucei* isolé de chiens au Nigeria

L'efficacité de Mel Cy (Cymelarsan, Rhône Mérieux, France) contre *Trypanosoma brucei* isolé de chiens a été étudiée chez des souris et des chien infectés expérimentalement. Les souris ont été infectées avec des parasites prélevés sur cinq chiens, puis traitées une fois par voie intrapéritonéale avec Mel Cy aux doses de 2,5 et 5,0 mg/kg, sept et 14 jours après l'infection, pour obtenir des indications sur la sensibilité du parasite au produit. Une récurrence de la parasitémie a été observée chez tous les lots de souris traitées 14 jours après l'infection, alors que presque toutes les souris traitées sept jours après l'infection n'ont pas présenté de parasitémie pendant la période d'observation de 63 jours. Cinq chiens ont été infectés avec une souche du parasite, puis traités les jours postinfection suivants : j7 (un chien), j14 (deux chiens) et j21 (deux chiens) à la dose de 2,5 mg/kg, par voie sous-cutanée et pendant deux jours consécutifs. Suite au traitement avec Mel Cy, des améliorations dans la condition clinique des chiens ainsi que des gains de poids ont été enregistrés. Une récurrence de l'infection n'a été observée que dans l'un des deux chien traités 14 jours postinfection. La parasitémie n'a été récurrente ni chez le chien traité sept jours postinfection ni chez ceux traités 21 jours postinfection. Il semble donc que Mel Cy soit efficace, aux doses utilisées dans cette étude, pour traiter la trypanosomose à *T. brucei* chez les chiens.

Mots-clés : Chien - Souris - *Trypanosoma brucei* - Cymelarsan - Trypanocide - Infection expérimentale - Nigeria.

Resumen

Anene B.M., Ogbuanya C.E., Mbah E.S., Ezeokonkwo R.C. Ensayo preliminar sobre la eficiencia de Cymelarsan en perros y ratones infectados en forma artificial con *Trypanosoma brucei* aislado en perros en Nigeria

La eficiencia de Mel Cy (Cymelarsan, Rhône Mérieux, France) contra *Trypanosoma brucei* aislado en perros fue estudiada en ratones y perros infectados en forma experimental. Los ratones fueron infectados con parásitos recolectados en cinco perros diferentes y tratados una vez, intraperitonealmente, con Mel Cy a una dosis de 2,5 y 5,0 mg/kg, 7 y 14 días después de la infección, esto con el fin de proporcionar un índice de la sensibilidad parasitaria. La recaída de la parasitemia se presentó en todos los grupos de ratones tratados 14 días post infección, mientras que casi todos los ratones tratados 7 días después de la infección permanecieron parasitologicamente negativos durante los 63 días del período de observación. Cinco de los perros fueron infectados con un lote del parásito y luego tratados en los siguientes días post infección: día 7 (un perro), día 14 (dos perros) y día 21 (dos perros) a una dosis sub cutánea de 2,5 mg/kg, en dos días consecutivos. Después del tratamiento con Mel Cy, se observaron mejoras en la condición clínica, así como ganancias de peso en los perros. Se presentó solamente una recaída en uno de los dos perros tratados 14 días post infección. Sin embargo, ni el perro tratado al día 7 ni los tratados al día 21 después de la infección recayeron. Por lo tanto parece que, al régimen de dosis utilizado en este estudio, el Mel Cy puede ser efectivo para el tratamiento de la tripanosomosis en perros debida a *T. brucei*.

Palabras clave: Perro - Raton - *Trypanosoma brucei* - Cymelarsan - Trypanocide - Infección experimental - Nigeria.