Rev. Inst. Med. trop. São Paulo
33 (1): 50-57, janeiro-fevereiro, 1991

Schistosoma mansoni: PRECLINICAL STUDIES WITH 9-ACRIDANONE-HYDRAZONES IN Cebus MONKEYS EXPERIMENTALLY INFECTED

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SUMMARY

Derivatives of acridine (9-Acridanone-hydrazones) were tested in **Cebus** monkeys experimentally infected with **Schistosoma mansoni**, at the dosages of 50, 25, and 12.5 mg/kg (p.o., single dose). At least, four compounds seemed to be very promising, promoting alterations in the oogram and reducing the worm burden drastically, even at the lowest dose (12.5 mg/kg). No side effects could be detected after drug administration.

KEY WORDS: Schistosoma mansoni; Chemotherapy; **Cebus** monkeys; 9-Acridanone-hydrazones; Active drug.

INTRODUCTION

In spite of the unquestionable value of various modern drugs against **Schistosoma mansoni**, the ideal antischistosomal compound — as recognized by WHO — was not obtained as yet. In this way, the ideal drug[5, 6, 11] could be summarized as follows; 1. no side effects and toxicity in man; 2. high activity against the three main schistosome infections; 3. efficient when given at a single oral dose; 4. active against all stages of the parasite in mammalian host, and 5. low price.

Nowadays, the most used drugs against different species of the genus **Schistosoma** in the world — Oxamniquine and Praziquantel present some advantages, such as: single dose, low toxicity, and chemical stability. Nevertheless, the therapeutic efficacy of oxamniquine has been questioned by some researcher-clinicians. In fact, SILVA et al[15] showed that oxamniquine, the most used schistosomicide drug in Brazil, does not promote the elimination of all the parasites. In addition, drug resistant strains of **S. mansoni** could be selected or induced by the administration of lower doses of schistosomicide compounds[2, 7, 14] or found naturally resistant to oxamniquine in some endemic areas[1, 3, 4, 8].

In some countries of Africa, the curative dose of oxamniquine was found to be 30 mg/kg, whereas in South America the curative dose is 15 mg/kg[18].

These comments strengthen the need for increasing the researches on experimental chemotherapy, aiming at finding more efficacious or alternative new antischistosomal drugs.

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Derivatives of acridine have been largely used for their antiseptic, antiprotozoal and antihelminthic properties. Some acridine derivatives are active against experimental **Schistosoma mansoni** infections in mice and hamsters[16]. High activity of some of these compounds (Ro-15.8843/000, Ro-16.2308/000, Ro-15.5458/000 and Ro-15.9268/000, at 25 mg/kg) was confirmed in baboons experimentally infected with **Schistosoma mansoni**[17].

In the present study, the above mentioned drugs were tested in **Cebus** monkeys, a well known primate model for studies on chemotherapy against **Schistosoma mansoni.**

MATERIAL AND METHODS

The **Cebus** monkeys used in this research were born and reared at the Zoo of São Paulo, Brazil, where they were crowded together, since these animals are very prolific under captivity conditions. For this reason, the Directors of the Zoo allowed us some specimens for this study.

The animals (adult, both sexes) were maintained in individual cages at the primate animal house, and fed on bred soaked in milk and fruits throughout the experiment.

They were infected two months before drug administration, with the LE strain of **Schistosoma mansoni.** The LE strain of **S. mansoni** was maintained for more than 25 years through hamster — **Biomphalaria glabrata** — hamster passages. Each monkey was restrained at dorsal decumbency on a table. Water containing about 200 cercariae per monkey was dropped gently over the abdomen and inguinal regions. After the incubation period, rectal snips from the **Cebus** monkeys were obtained and submitted to the oogram technique[9, 10, 12]. This procedure was performed weekly, until the end of the experiment. Immature (four stages), and mature egg counts were performed on the rectal snips, the results being expressed in numbers of viable eggs/gram of rectal tissue. In the same period of the oograms, stool examinations were carried out weekly, by the sedimentation technique, this procedure being maintained for at least 20 weeks after treatments.

The chemical structure of the compounds used in the experiment is presented in Fig. 1. Some monkeys were chosen for controls in one experiment. In some cases, the control monkey of one experiment was used in a second one for drug administration. In a few cases, a monkey treated with a non active compound was carefully inspected and, if the oogram remained stable for some months, it could be used for treatment with another compound.

In the same way, a monkey treated and cured was reused after a successful reinfection. This procedure was necessary since it is very difficult to obtain **Cebus** monkeys for medical research.

Drugs were suspended in an aqueous solution of gum arabic, and given orally, at a single dose (see tables 1, 2 and 3). Careful inspection in animals was done to detect signs of toxicity, during one week after treatment. Some compounds, despite showing high activity in the first treatment, were not used in further experiments with lower doses, due to a number of properties as drug chemical instability.

Some monkeys, according to the results of the oogram, were perfused for worm counting and microscopical examinations of the tissues. Necropsies were carried out after an overdose of pentobarbital. The animals were submitted to perfusion of the portal hepatic system according to PELLEGRINO & SIQUEIRA[13].

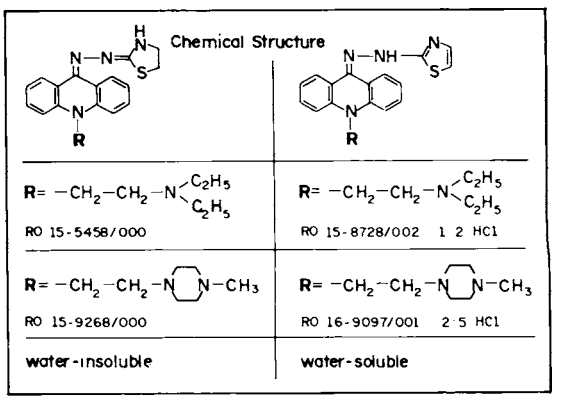

Fig. 1 — Derivatives of acridine (9-Acridanone-hydrazones): chemical structure.

TABLE 1

Chemotherapy with 9-acridanone-hydrazone drugs in the experimental schistosomiasis in **Cebus** monkeys (P.O., 50 mg/kg, single doses).

Monkeys	Days before (−) or after (+) treatment	Oogram (egg stages)					Number of viable eggs per gram of rectal tissue
		1st	2nd	3rd	4th	Mature	
A-10	− 6	57	45	67	109	280	9.300
Treated with	+ 8	0	4	6	37	290	7.659
Ro-15.8728/002	+ 15	0	0	0	0	9	270
	+ 22	0	0	0	0	0	0
	+ 29	0	0	0	0	0	0
	+ 43	0	0	0	0	0	0
Oograms performed at days + 57, + 85, + 97, + 120, + 135, did not detect viable eggs.							
H-1	− 6	1	0	5	0	9	416
Treated with	+ 8	0	0	0	0	33	767
Ro-15.9268/000	+ 15	0	0	0	0	0	0
	+ 22	0	0	0	0	0	0
	+ 29	0	0	0	0	0	0
	+ 43	0	0	0	0	0	0
Oograms performed at days + 57, + 85, + 97, + 120, + 135, did not detect viable eggs.							
A-5	− 6	63	31	122	53	199	9.000
Treated with	+ 8	0	0	12	31	719	10.438
Ro-16.9097/001	+ 15	0	0	0	0	22	478
	+ 22	0	0	0	0	0	0
	+ 29	0	0	0	0	0	0
	+ 43	0	0	0	0	0	0
Oograms performed at days + 57, + 85, + 97, + 120, + 135, did not detect viable eggs.							
H-5	− 6	16	0	2	2	45	2.600
Treated with	+ 8	0	0	0	0	156	1.763
Ro-15.5458/000	+ 15	0	0	0	0	23	354
	+ 22	0	0	0	0	3	49
	+ 29	0	0	0	0	0	0
	+ 43	0	0	0	0	0	0
Oograms performed at days + 57, + 85, + 97, + 120, + 135, did not detect viable eggs.							
H-2	− 6	83	19	17	18	57	5.542
Treated with	+ 8	127	129	188	147	368	10.312
Ro-15.8043/001	+ 15	47	19	53	63	447	8.064
	+ 22	10	2	60	31	227	4.583
	+ 29	37	7	9	13	123	3.500
	+ 43	26	53	42	27	92	3.429
	+ 57	49	33	133	53	180	8.784
	+ 85	82	87	189	80	383	10.907
	+ 97	78	72	42	62	351	8.521
	+ 120	9	0	14	6	320	8.116
	+ 135	14	6	72	89	42	5.575
H-3 (Control)	− 6	0	0	9	0	21	698
	+ 8	10	0	13	20	94	2.740
	+ 15	0	14	12	14	63	2.572
	+ 22	13	37	47	63	153	4.230
	+ 29	18	7	83	26	239	6.661
	+ 43	70	15	106	49	196	6.228
	+ 57	26	4	64	48	217	8.756
	+ 85	17	0	31	21	164	4.315
	+ 97	30	9	14	14	80	4.594
	+ 120	41	101	99	111	285	10.948
	+ 135	15	9	104	47	125	6.818

TABLE 2

Chemotherapy with 9-acridanone-hydrazone drugs in the experimental schistosomiasis in **Cebus** monkeys (P.O., 25 mg/kg, single doses).

Monkeys	Days before (−) or after (+) treatment	Oogram (egg stages)					Number of viable eggs per gram of rectal tissue
		1st	2nd	3rd	4th	Mature	
H-2	− 15	0	1	25	0	16	1.313
Treated with	− 2	1	6	42	6	32	2.231
Ro-16.2308/000	+ 7	0	0	0	0	0	0
	+ 14	0	0	0	0	0	0
	+ 28	0	0	0	0	0	0
	+ 42	0	0	0	0	0	0
Oograms performed at days + 70, + 97, + 134, + 158 did not detect viable eggs.							
H-6	− 15	12	0	20	24	160	6.781
Treated with	− 2	14	19	48	40	94	4.479
Ro-15.5458/000	+ 7	0	2	0	4	25	1.292
	+ 14	0	0	0	0	1	50
	+ 28	0	0	0	0	0	0
	+ 42	0	0	0	0	0	0
Oograms performed at days + 70, + 97, + 134, + 158 did not detect viable eggs.							
H-7	− 15	39	1	7	66	322	8.208
Treated with	− 2	8	0	2	20	134	5.655
Ro-15.9268/000	+ 7	0	0	0	0	87	2.807
	+ 14	0	0	0	0	6	272
	+ 28	0	0	0	0	0	0
	+ 42	0	0	0	0	0	0
Oograms performed at days + 70, + 97, + 134, + 158 did not detect viable eggs.							
H-10	− 15	20	14	32	45	28	2.139
Treated with	− 2	28	110	122	126	318	14.667
Ro-15.8843/000	+ 7	0	0	0	0	18	367
	+ 14	0	0	0	0	5	106
	+ 28	0	0	0	0	1	39
	+ 42	0	0	0	0	0	0
Oograms performed at days + 70, + 97, + 134, + 158 did not detect viable eggs.							
H-9	− 15	50	34	72	72	79	5.533
Treated with	− 2	11	20	150	118	508	15.519
Ro-14.1587/000	+ 7	53	2	1	60	221	6.358
	+ 14	48	25	8	98	299	11.950
	+ 28	0	0	9	1	5	395
	+ 42	53	9	9	27	141	7.710
	+ 70	70	51	85	46	275	13.868
	+ 97	22	33	45	14	144	6.450
	+ 134	12	1	74	8	206	7.167
	+ 158	52	36	54	41	95	9.267
A-5 (Control)	− 15	109	90	60	109	673	16.524
	− 2	118	56	144	128	620	25.381
	+ 7	92	34	81	90	542	22.676
	+ 14	53	54	98	29	274	14.111
	+ 28	25	32	70	161	448	21.029
	+ 42	58	8	30	23	220	13.560
	+ 70	13	3	6	33	241	7.220
	+ 97	25	8	52	60	119	6.140
	+ 134	33	16	7	64	80	5.618
	+ 158	18	7	32	63	214	13.133

TABLE 3

Chemotherapy with 9-acridanone-hydrazone drugs in the experimental schistosomiasis in **Cebus** monkeys (P.O., 12.5 mg/kg, single doses).

Monkeys	Days before (−) or after (+) treatment	Oogram (egg stages)					Number of viable eggs per gram of rectal tissue
		1st	2nd	3rd	4th	Mature	
H-11	− 15	181	42	133	98	114	10.923
Treated with	− 7	80	62	67	179	287	15.067
Ro-15.5458/000	+ 7	2	2	89	72	355	12.820
	+ 15	0	0	0	3	21	522
	+ 30	0	0	0	0	0	0
	+ 45	0	0	0	0	0	0
Oograms performed at days + 60, + 72, + 93, + 106, + 136, + 151 did not detect viable eggs.							
H-12	− 15	19	17	0	21	99	2.516
Treated with	− 7	9	22	18	14	24	1.526
Ro-15.8843/000	+ 7	0	1	2	3	76	2.278
	+ 15	0	0	0	0	6	200
	+ 30	0	0	0	0	0	0
	+ 45	0	0	0	0	0	0
Oograms performed at days + 60, + 72, + 93, + 106, + 136, + 151 did not detect viable eggs.							
H-13	− 15	3	0	0	0	28	775
Treated with	− 7	42	10	38	83	77	6.250
Ro-15.9268/000	+ 7	16	38	31	9	211	7.093
	+ 15	0	0	0	0	26	605
	+ 30	0	0	0	0	0	0
	+ 45	0	0	0	0	0	0
Oograms performed at days + 60, + 72, + 93, + 106, + 136, + 151 did not detect viable eggs.							
H-14	− 15	38	11	33	5	74	3.426
Treated with	− 7	37	30	24	45	127	4.598
Ro-16.2308/000	+ 7	63	31	48	3	114	6.475
	+ 15	0	0	0	0	2	63
	+ 30	0	0	0	0	0	0
	+ 45	0	0	0	0	0	0
Oograms performed at days + 60, + 72, + 93, + 106, + 136, + 151 did not detect viable eggs.							
H-9 (Control)	− 15	6	0	0	4	99	5.450
	− 7	9	4	5	42	21	2.914
	+ 7	51	4	50	111	109	13.542
	+ 15	32	14	39	70	55	9.130
	+ 30	51	26	59	70	296	13.944
	+ 45	6	0	1	48	161	7.700
	+ 60	13	1	5	2	2	1.150
	+ 72	85	38	37	50	127	15.045
	+ 93	2	1	8	8	71	2.857
	+ 106	9	30	4	0	81	3.949
	+ 136	46	71	22	45	150	12.388
	+ 151	12	17	32	15	141	6.536
A-5 (Control)	− 15	107	15	28	44	134	7.628
	− 7	77	49	59	78	179	10.006
	+ 7	18	6	24	8	154	6.364
	+ 15	42	14	55	117	60	4.721
	+ 30	160	19	82	28	250	12.833
	+ 45	15	23	19	27	195	7.750
	+ 60	0	31	13	53	37	4.012
	+ 72	53	10	56	13	86	5.450
	+ 93	49	34	53	57	35	7.808
	+ 106	15	38	128	21	101	8.234
	+ 136	38	81	77	22	66	8.045
	+ 151	14	61	60	76	116	7.332

RESULTS

Results of treatment against schistosomiasis mansoni in **Cebus** monkeys with 9-Acridanone-hydrazones, dosed 50 mg/kg body weight, are summarized in Tables 1 (oogram) and 4 (worms recovered after necropsies). As can be seen, four compounds (Ro-15.8728/002, Ro-15.9268/000, Ro-16.9097/001 and Ro-15.5458/000) proved to be very active, suppressing the early stages of the parasite eggs found in oograms of rectal snips from monkeys A-10, H-1, A-5 and H-5, respectively. Later, even mature eggs could not be found and the oograms remained negative until the last observation (day + 135). Compound Ro-15.8043/001 failed to cure monkey H-2, its oogram presenting viable eggs throughout the observation period, the same occurring with monkey H-3 (control). In addition, the stool examinations carried out weekly from day + 43 to day + 135 were also negative for monkeys A-10, H-1, A-5, and H-5 paralleling the oogram findings. Monkeys H-2 and H-3 always presented viable eggs in all the stool examinations, for the same period. Monkeys H-1 and H-5 were sacrificed, at the end of the experiment. They presented intestinal viscerae with normal appearance, and no viable eggs were found in the liver. Only monkey H-1 presented a single female worm recovered from mesenteric vessels through perfusion. This worm presented degeneration of the genital system with an abnormal egg in the uterus (Table 4).

Following the first study in monkeys treated with 50 mg/kg, the second experiment used 25 mg/kg body weight, **per os**, single dose. Compounds tested were Ro-16.2308/000, Ro-15.5458/000, Ro-15.9268/000, Ro-15.8843/000, and Ro-14.1587/000, for infected **Cebus** monkeys H-2 (previously tested with compound Ro-15.8043/001, but with no signs of drug activity), H-6, H-7, H-10, and H-9, respectively. Monkey A-5 (previously treated with Ro-16.9097/001, cured and reinfected) served as control. A strong activity, early detected, with complete disappearance of viable eggs was found in rectal snips from monkeys H-2, H-6, H-7 and H-10, and all the coproscopic examinations remained negative too, throughout the experimental period. In sharp contrast, monkey H-9 (compound Ro-14.1587/000) was not cured, its oogram (table 2) presenting a similar pattern as that from control (monkey A-5). Results of necropsies of monkeys treated with the compounds dosed 25 mg/kg are summarized in table 4. As can be seen, compounds Ro-16.2308/000 and Ro-15.9268/000 killed all the worms. The primates treated with Ro-15.8843/000 and Ro-15.5458/000 show only few male worms.

Results of treatment using 9-Acridanone-hydrazones at 12.5 mg/kg (p.o., single dose) showed the same efficacy in curing monkeys H-11 (Ro-15.5458/000), H-12 (Ro-15.8843/000), H-13 (Ro-15.9268/000), and H-14 (Ro-16.2308/000), both by oogram of rectal biopsies and through stool

TABLE 4
Results of perfusion of **Cebus** monkeys treated with 9-Acridanone-hydrazone drugs.

Monkey	Drug	Dose (mg/kg)	Days after treatment	Worm recovery		
				Mesentery	Liver	Total
H-1	Ro-15.9268/000	50	180	1 F	0	1
H-5	Ro-15.5458/000	50	180	0	0	0
H-2	Ro-16.2308/000	25	162	0	0	0
H-6	Ro-15.5458/000	25	169	1 M	0	1
H-7	Ro-15.9268/000	25	169	0	0	0
H-10	Ro-15.8843/000	25	162	4 M	2 M	6
H-11	Ro-15.5458/000	12.5	186	0	0	0
H-12	Ro-15.8843/000	12.5	186	1 M	1 M	2
H-13	Ro-15.9268/000	12.5	187	0	0	0
H-14	Ro-16.2308/000	12.5	187	2 M 1 F	0	3

M = Male worm; F = Female worm.

examinations for the whole period of investigation (table 3). The controls H-9 (previously treated with Ro-14.1587/000, 25 mg/kg, but not cured) and A-5 (also used as control in experiments with compounds dosed 25 mg/kg), presented viable eggs and positive stool examinations, until the end of the experiment (day + 151). Results from necropsies are summarized in table 4. Again, no trematodes were found in two monkeys (H-11 and H-13), the other two primates showing very few remaining worms.

No signs of toxicity were observed in all the monkeys, at every dosage, following a week after drug administration.

DISCUSSION

From the experiments, four 9-Acridanone-hydrazone compounds proved to be very active (Ro-15.5458/000, Ro-15.8843/000, Ro-15.9268/000 and Ro-16.2308/000), in curing the experimental schistosomiasis mansoni of **Cebus** monkeys (p. o., single dose). Activity was early detected through the oograms, by the absence of the parasite's eggs (all viable stages) in rectal snips, and relapses were not found over four months of weekly observation, also confirmed by the absence of **Schistosoma mansoni** eggs in feces after the 43rd day of treatment (at those doses, it is inferred the compounds do not interfere in the maturation of eggs already laid — the usual finding of most antischistosomal drugs). The absence or, in some cases, the presence of very few remaining schistosomes, usually male worms, also demonstrate the strong activity of these compounds.

Because no side effects were observed and due to the strong antischistosomal activity showed, 9-Acridanone-hydrazones may be considered as very promising compounds against **Schistosoma mansoni** infection, as stated in this preclinical study. If approved after extensive toxicological tests, they possibly will be accepted for clinical trials.

RESUMO

Schistosoma mansoni: estudos pré-clínicos com 9-acridanona-hidrazonas em macacos Cebus experimentalmente infectados.

Derivados de acridina (9-acridanona-hidrazonas) foram testados em macacos **Cebus** experimentalmente infectados com **Schistosoma mansoni**, nas doses de 50, 25 e 12,5 mg/kg, em dose única, via oral. Quatro compostos, pelo menos, mostraram-se muito promissores, causando alterações no oograma e reduzindo drasticamente a carga de vermes, mesmo quando a dose mais baixa (12,5 mg/kg) foi usada. Efeitos colaterais não foram detectados após administração da droga.

ACKNOWLEDGEMENT

We thank Dr. H. R. Stohler (F. Hoffmann-La Roche & Co. Ltd., Basle, Switzerland) for providing compounds used in this research, as well as for financial support and advice; Dr. Faiçal Simon and Dr. Adayr Mafuz Saliba (Fundação Parque Zoológico de São Paulo) for the supply of **Cebus** monkeys utilized in this study; Mr. Adelino Ferreira, Mrs. Alice N. Faria, Mr. Alberto G. Santos, Mr. Maurício V. Costa, and Miss Zenir de Souza for technical assistance.

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Recebido para publicação em 16/5/1990.
Aceito para publicação em 13/9/1990.