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ANTISCHISTOSOMAL ACTIVITY OF ACRIDANONE-HYDRAZONES IN *CEBUS* MONKEYS EXPERIMENTALLY INFECTED WITH THE SJ STRAIN OF *SCHISTOSOMA MANSONI*

Paulo Marcos Zech Coelho, Leógenes Horácio Pereira† and Rômulo Teixeira de Mello

In this study, four compounds were utilized at the dose of 12.5mg/kg body weight, p.o., to treat Cebus *monkeys experimentally infected with about 200 cercariae of* Schistosoma mansoni *(SJ strain), via transcutaneous route. The oograms performed with rectal snips, as well as stool examinations carried out periodically, showed no viable eggs of the parasite, from day 29 to 226 post-treatment. The perfusion undertaken after killing the animals showed absence of worms in the treated monkeys, whereas 83 worms were recovered from the control, thus corroborating the results obtained by means of oograms and coproscopy. These results confirm the efficacy of 9-acridanone-hydrazones previously tested against the LE strain of* S. mansoni. *The low curative dose and apparent absence of toxicity render these drugs an important therapeutic reserve, taking into consideration the reports on the resistance of* S. mansoni *to the modern drugs oxamniquine and praziquantel.*

Key-words: Schistosoma mansoni. Cebus *monkeys. Acridanone-hydrazone*

Although much effort has been directed toward the improvement of the chemotherapy for schistosomiasis mansoni, and despite the large progress obtained in this field, curative treatment of this disease with the already known standard antischistosomal compounds presents some difficulties. The high price of drugs, drug side effects, cases of drug resistance, among other problems, point toward the continuous search for new active substances.

Coelho and Pereira[4] showed a promising activity of 9-acridanone-hydrazone compounds in *Cebus* monkeys experimentally infected with the LE strain of *Schistosoma mansoni.*

However, a question arises whenever new promising compounds against schistosomiasis appear. Are they effective against all human schistosomiasis, and even if active against a strain of a specific species (*S. mansoni*, for instance), can their effectiveness be extended to other strains? It is well known that *S. mansoni*, mainly in some countries of Africa, presents different susceptibilities to chemotherapy with oxamniquine, via oral route. Thus, in Brazil and West Africa, 15mg/kg body weight is the dosage commonly used, whereas in East Africa the effective dose ranges from 30 to 45mg/kg, and in Egypt doses of up to 60mg/kg given over three days are required[16]. On the other hand, the resistance against oxamniquine by *S. mansoni* has been detected in Brazilian patients[1 6]. Cioli et al[3] clearly showed that this resistance was controlled by a single autosomal recessive gene.

In Brazil, three species of *Biomphalaria* mollusks are responsible for the natural transmission of schistosomiasis mansoni, and these species are predominant as vectors in different areas. Thus, the adaptation between some strains of the parasite and the geographical strains of snails[2 8 10 11] has been demonstrated, as well as the variation in the pathogenicity degree related to strains of *S. mansoni* has been proved[5 13 15].

The purpose of the present work, using the *Cebus* monkey model, is to verify whether the

Departamentos de Parasitologia, Instituto de Ciências Biológicas, e de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte, MG.
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† Deceased 6 February, 1994
Endereço para correspondência: Prof. Paulo Marcos Zech Coelho, Depto de Parasitologia. ICB/UFMG/Caixa Postal 486, 30161-970 Belo Horizonte, MG.
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SJ strain of *S. mansoni* (isolated in the State of São Paulo, in an area where *Biomphalaria tenagophila* is the snail vector) presents the same susceptibility to the acridanone-hydrazones utilized against the LE strain of the parasite (isolated in the State of Minas Gerais, in an area where *Biomphalaria glabrata* is the snail vector), using the *Cebus* monkey model too.

MATERIAL AND METHODS

Capuchin monkeys (*Cebus sp*), adults of both sexes, were maintained in individual cages in the animal house. The monkeys were fed on daily with bred soaked in milk, fruit, and standard pellet food. They were infected with about 200 cercariae of *S. mansoni* (SJ strain), transcutaneously. The life cycle of the trematode was maintained at the laboratory through hamster - *Biomphalaria tenagophila* - hamster passages. Acridanone-hydrazone drugs were given after the mature infection had been stablished. The monkeys that were found to be positive (presenting large numbers of schistosome eggs in the stools and in rectal snips) were selected for the experiments. The compounds Ro-15.5458/000, Ro-15.8843/000, Ro-15.9268/000 and Ro-16.2308/000 (Figure 1) were administered at the dosage of 12.5mg/kg body weight, by oral route, single dose. The infected monkey E-2 was kept as control. The quantitative oogram of rectal snips[9], stool examination[4], and perfusion of portal system for worm recovery12 were used as criteria for determination of parasitological cure.

RESULTS

It must be emphasized that the coproscopies performed confirmed the oogram in rectal snips in all cases.

The drug effects against the SJ strain of *S. mansoni* are summarized in Table 1. The stool examination and perfusion of portal system of the monkeys confirmed the findings obtained with the rectal snips. So, when all the treated monkeys were examined (26 examinations per monkey) no eggs could be detected in stool examinations. On the other hand, the presence of viable eggs was detected in all the stool examinations of the control monkey. No worms could be detected through perfusion into the treated monkeys, whereas 83 worms (24 females and 59 males) were recovered from the control monkey (E-2).

DISCUSSION

Some 9-acridanone-hydrazones have been proved very effective in the preclinical treatment for schistosomiasis, when nonhuman

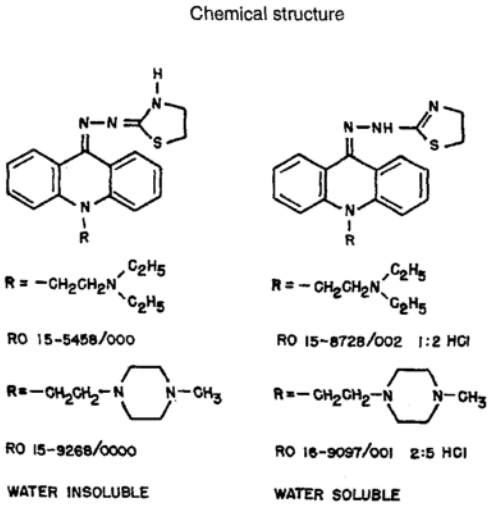

Figure 1 - Chemical structures of the 9-acridanone-hydrazone compounds drugs used in this work.

Table 1 - Chemotherapy with 9-Acridanone-hydrazone compounds in Cebus *monkeys experimentally infected with the SJ strain of* Schistosoma mansoni.

Monkeys	Days before (-) or after (+) treatment	Oogram (egg stages)					Dead eggs	Number of viable eggs per gram of rectal tissue
		1st	2nd	3rd	4th	Mature		
E-2	- 8	8	5	2	1	22	24	1151
(Control)	- 1	4	1	2	0	8	5	325
	+ 14	149	54	47	41	96	55	8096
	+ 29	37	28	70	51	265	29	13072
	+ 44	80	12	41	120	184	30	9296
	+ 58	32	16	47	125	175	70	7900
	+ 71	28	9	27	34	40	60	4313
	+ 85	26	16	36	15	144	46	9480
	+ 97	29	50	101	64	148	74	8000
	+112	1	11	10	24	84	48	5417
	+128	32	1	5	36	121	17	7222
	+142	19	25	21	49	142	101	10667
	+152	38	15	91	179	311	93	14089
	+167	52	3	65	189	229	41	19656
	+196	13	15	90	42	220	44	8750
	+211	102	70	128	167	389	65	25206
	+226	44	23	58	116	114	23	10350
* E-3	- 8	1	2	8	1	57	3	1169
Treated with	- 1	0	1	5	8	27	13	719
Ro-15.5458/000	+ 14	0	0	0	0	4	3	94
12.5mg/kg, p.o	+ 29	0	0	0	0	0	2	0
	+ 44	0	0	0	0	0	0	0
	+ 58	0	0	0	0	0	0	0
* E-4	- 8	5	7	1	0	72	18	2125
Treated with	- 1	3	2	9	8	59	23	1528
Ro-15.8843/000	+ 14	0	0	0	0	2	7	52
12.5mg/kg, p.o.	+ 29	0	0	0	0	0	1	0
	+ 44	0	0	0	0	0	0	0
	+ 58	0	0	0	0	0	0	0
* E-5	- 8	6	13	1	9	62	10	1468
Treated with	- 1	5	4	5	10	58	38	1344
Ro-15.9268/000	+ 14	0	0	0	0	1	10	21
12.5mg/kg, p.o.	+ 29	0	0	0	0	0	3	0
	+ 44	0		0	0	0	0	0
	+ 58	0		0	0	0	0	0
* E-6	- 8	2	10	35	18	67	18	1941
Treated with	- 1	16	59	57	30	186	58	6327
Ro-16.2308/000	+ 14	0	0	0	0	4	19	72
12.5mg/kg, p.o.	+ 29	0	0	0	0	0	12	0
	+ 44	0	0	0	0	0	0	0
	+ 58	0	0	0	0	0	0	0

* Oograms performed in the treated monkeys (E-3, E-4, E-5 and E-6), at days +71, +85, +97, +112, +128, +142, +152, +167, +196, +211 and +226, did not detect viable eggs.

primate models, as baboons[14] and *Cebus* monkeys[4], were used. Very good results have been reported by Coelho and Pereira[4] using *Cebus* monkeys infected with the LE strain of *S. mansoni*, and treated with some acridanone-hydrazones that showed curative activity at doses as low as 25mg, sometimes 12.5mg, per os, single administration. These authors showed that the results obtained through periodical rectal biopsies and stool examinations carried out prior and up to six months after treatment were really curative. In some cases, some treated simians (negative for coproscopies and rectal biopsies) were sacrificed at that time, and few or no worms could be found after the portal system perfusion, thus showing that the laboratory findings were not due to chemical sterilization of the worms but, in fact, were associated with the consequent death of the parasites. In that

occasion, it was verified that the curative doses, besides being quite low, and singly orally administered, did not show visible side effects on the primates.

In the same work, it has been observed a marked activity of all the compounds studied against the SJ strain of *S. mansoni*, at a lower dose (12.5mg/kg), thus confirming the results obtained by Coelho and Pereira[4] with the LE strain. These results lead the authors to think on the possibility of the same compounds being successful in a lower curative dose (less than 12.5mg/kg body weight in *Cebus* monkeys). It is well known that many schistosomicides in the monkey require near five times more dosing than that used for man. Thus it seems that doses lower than 3mg/kg body weight could possibly be used for man, although it must be proved whether the toxicity of these compounds does not prevent their use in humans.

The report on drug resistance related to the use of oxamniquine, the most utilized drug in the treatment for schistosomiasis in Brazil[1,7], widen the possibility of considering the drugs here studied as an important reserve supply to be used, perhaps, in the near future.

RESUMO

No presente trabalho, quatro compostos foram utilizados na dose de 12,5mg/kg de peso, por via oral, em macacos infectados transcutaneamente com cerca de 200 cercárias de Schistosoma mansoni. *Os oogramas realizados com fragmentos de mucosa retal e os exames de fezes realizados, periodicamente, demonstraram a ausência de ovos viáveis do parasito a partir do 29º até o 226º dia pós-tratamento. A perfusão, após sacrifício dos animais tratados, não detectou vermes, enquanto que do macaco controle 83 vermes foram recuperados, confirmando assim os resultados dos oogramas e da coproscopia. Estes resultados confirmam a eficácia das 9-acridanonas-hydrazonas já observada anteriormente contra a cepa LE de* S. mansoni. *A baixa dosagem curativa e aparente ausência de toxicidade colocam estas drogas como uma reserva terapêutica importante, tendo em vista o relato de resistência do* S. mansoni *às drogas modernas oxamniquina e praziquantel.*

Palavras-chaves: Schistosoma mansoni. *Macacos* Cebus. *Acridanona-hidrazonas.*

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