Rev. Inst. Med. trop. São Paulo
19(1):43-46, *janeiro-fevereiro,* 1977

UDC 616.995.122.22

CHEMOPROPHYLACTIC ACTIVITY OF KNOWN SCHISTOSOMICIDAL AGENTS

J. PELLEGRINO (1,2), Leógenes H. PEREIRA (1) and Rômulo T. MELLO (1)

SUMMARY

The chemoprophylactic activity of 17 antischistosomal compounds was evaluated in mice experimentally infected with **Schistosoma mansoni.** All but 2 compounds (Hycanthone and Oxamniquine), administered as a single dose, were given for 5 consecutive days (starting 3 hours before exposure and continuing for the following 4 days), each dose corresponding to about 1/5 of the LD_{50}. Animals were exposed to 200 cercariae, sacrificed 30 days after infection, and the worms collected by perfusing the liver and mesenteric vessels. In mice treated with Hoechst S-616 and S-688, Ciba 17'581, RD 12,869 and Oxamniquine, no schistosomes were found. Treatment with A-16,612, Lucanthone, Mirasan and Hycanthone produced a statistically significant reduction ($p \leq 0.05$) of worm burden.

INTRODUCTION

It has been shown that, as a general rule, adult schistosomes are more sensitive than juvenile forms to different classes of antischistosomal agents: **antimonials** (SCHUBERT [13]; LUTTERMOSER [6]; STANDEN [15]; BRENER & CHIARI [1]; STOHLER & FREY [17, 18]); **Hoechst S-688** and **S-616** (DE MEILLON et al. [2]; LÄMMLER [5]; LUTTERMOSER et al.[7]); **p-aminodiphenoxyalkanes** (STANDEN[14]); **tris** (p-aminophenyl) **carbonium salts** (THOMPSON et al.[19]); **Niridazole** (LAMBERT & STAUFFER [4]; LAMBERT [3]; SADUN et al. [12]; YOKOGAWA et al.[20]).

In the present study the chemoprophylactic activity of 17 known schistosomicidal agents was evaluated, the drugs being administered by subcutaneous, oral or intramuscular route. With the exception of Fouadin and Tartar emetic, all compounds used had been already tested against schistosomula developed in the peritoneal cavity of mice (PEREIRA, PELLEGRINO & MELLO [10]).

MATERIALS AND METHODS

Antischistosomal agents — The chemical names of the compounds included in the present study have been mentioned in previous papers (PELLEGRINO & FARIA [8] and PEREIRA, PELLEGRINO & MELLO [10]). Hycanthone and Oxamniquine were given as a single dose (80 and 200 mg/kg, respectively) by intramuscular route, 3 hours before exposure to cercariae. As far as possible, all other compouds were administered at a daily dose level corresponding to 1/5 of the acute LD_{50} for mice (PELLEGRINO & FARIA [8]). The schedule of treatment consisted in 5 daily doses, the first, 3 hours before infection of mice and the others on the following days.

Infection of mice — The animals were exposed, by tail immersion (PELLEGRINO & KATZ [9]), to 200 ± 20 cercariae of **S. mansoni** (L. E. strain, Belo Horizonte).

Assessment of activity — All animals, including the control group, were sacrificed 30 days after infection, the liver and mesenteric vessels being perfused for worm counts. Worm

This work was supported, in part, by research grants from the «Conselho Nacional de Pesquisas», Brazil and WHO, Geneva, Switzerland

(1) Schistosomiasis Research Unit, Institute of Biological Sciences, Federal University of Minas Gerais
(2) «Centro de Pesquisas René Rachou, INERu-FIOCRUZ», Belo Horizonte
Contribution number 67 from the Schistosomiasis Research Unit
Address for reprints: C. Postal 1404. 30.000 Belo Horizonte, Brazil

burdens were calculated considering the control equal to 100.

RESULTS AND COMMENTS

The results obtained are summarized in Table I. As can be seen, with 5 compounds (Hoechst S-616, Ciba 17'581, RD 12,869, Hoechst S-688 and Oxamniquine) no schistosomes could be found after perfusion. These data are in agreement with the results obtained by PEREIRA, PELLEGRINO & MELLO [10] using as "targets" schistosomula developed into the peritoneal cavity of mice. A significant reduction ($p \leq 0.05$) in worm burden occurred after treatment with A-16,612, Lucanthone, Mirasan and Hycanthone. Tartar emetic and Fouadin proved very toxic. No significant prophylactic activity could be observed with Antiomaline, Hoechst S-201, Trichlorphone, Wellcome 153 C 51, Sb EDTA and Schistocide T-109. In comparing the present data with those reported by PEREIRA, PELLEGRINO & MELLO [10], discrepant results occurred only with Mirasan and Lucanthone (both inactive against peritoneal schistosomula).

It has been already mentioned that drugs tend to be less effective against juvenile schistosomes than sexually mature ones. Increase in dose level can produce response from progressively immature stages but, as stressed by STANDEN [16] experimental evidence indicates that activity differential as between adult and juvenile is not simply quantitative in terms of dose.

LÄMMLER [5] demonstrated that Hoechst S-616 and S-688 compounds are effective for a short period during the early schistosomule stage, later inactive against juvenile forms and again effective against mature worms. It is worth to emphasize that the majority of known antischistosomal agents were found active in the early schistosomular stage both by the method presented here and by the technique of PEREIRA et al. [11].

TABLE I

Chemoprophylactic activity of known antischistosomal agents. Mice were exposed to 200 cercariae of **Schistosoma mansoni** (tail immersion). Treatment was performed before (3 hr) and 1, 2, 3, and 4 days after exposure. All animals were sacrificed 30 days after infection.

Compounds	Route	Dead animals /Total	Daily dose (mg/kg) for 5 consecutive days	Schistosomes per mice	Mean worm burden /control = 100
Antiomaline	sc	0/10	18	54-54-27-40- 0-58-56- 8-43-23	91.2
Hoechst S-201	sc	0/10	1000	26-30-66-78-59-27-26-48-52-27	110.3
Fouadin	sc	5/10	280	44-10- 2-35-10	50.8
SB-EDTA	sc	2/10	100	13-22-10-14- 2- 6-19- 3	27.9
Tartar emetic	sc	8/10	9	3- 2	6.3
Hoechst S-616	sc	0/10	100	0- 0- 0- 0- 0- 0- 0- 0- 0- 0	0.0
Ciba 17'581	sc	0/10	760	0- 0- 0- 0- 0- 0- 0- 0- 0- 0	0.0
RD-12,869	sc	0/10	100	0- 0- 0- 0- 0- 0- 0- 0- 0- 0	0.0
A-16,612	sc	0/10	200	0- 3- 0- 0- 0- 0- 0- 0- 0- 0	0.8
Hoechst S-688	sc	0/10	350	0- 0- 0- 0- 0- 0- 0- 0- 0- 0	0.0
Lucanthone	sc	0/10	250	0- 2- 0- 8- 6- 2- 4- 8- 8-13	12.8
Schistocide T-109	sc	0/10	100	9-23-35- 6-27-30-21-22-16-22	53.0
Trichlorphone	sc	0/10	200	43-19-43-35-37-59-46-15- 3-27	82.2
Wellcome 153C51	sc	0/10	100	2-39-26-13-60-49-49-73-68-13	98.5
Mirasan	sc	0/10	100	0- 6- 0- 1- 8- 1- 4- 5- 4- 3	8.0
Hycanthone (*)	im	2/10	80	6-10- 9-21-27-36-43-15	52.5
Oxamniquine (*)	im	0/10	200	0- 0- 0- 0- 0- 0- 0- 0- 0- 0	0.0
Control	—	0/10	—	60-26-67-17-13-42-26-46-57-44	100.0

(*) single dose

PELLEGRINO, J.; PEREIRA, L. H. & MELLO, R. T. — Chemoprophylactic activity of known schistosomiasis agents. **Rev. Inst. Med. trop. São Paulo 19**:43-46, 1977.

RESUMO

Atividade quimioprofilática de agentes esquistossomicidas conhecidos

A ação quimioprofilática de 17 compostos esquistossomicidas foi testada em grupos de 10 camundongos previamente infectados, por via transcutânea, com 200 cercárias de **Schistosoma mansoni.** Com exceção de duas drogas, que foram administradas em dose única, as demais foram dadas em 5 doses diárias correspondentes, cada uma, a 1/5 da LD_{50}. Após 30 dias de infecção, os animais foram sacrificados e perfundidos para a coleta de esquistossomos localizados no fígado e vasos mesentéricos.

Os animais tratados com os compostos Hoechst S-616 e S-688, Ciba 17'581, RD-12869, Oxamniquine, A-16612, Lucanthone, Mirasan e Hycanthone apresentaram uma redução estatísticamente significativa do número de esquistossomos, sendo que nos 5 primeiros não foi encontrado nenhum verme. Os dados apresentados concordam, na sua quase totalidade, com aqueles anteriormente relatados, quando o critério de atividade adotado foi a redução do número de esquistossômulos desenvolvidos no peritôneo de camundongos.

REFERENCES

1. BRENER, Z. & CHIARI, E. — Ação da Fuadina e do Miracil D sobre os estádios iniciais de desenvolvimento do **Schistosoma mansoni** no camundongo. **Rev. Brasil. Malar. Doenças Trop. 9**: 485-488, 1957.

2. DE MEILLON, B.; ENGLAND, E. C. & LÄMMLER, G. — Experimental bilharziasis in animals. IV — Chemoprophylaxis in bilharziasis. **S. Afr. Med. J. 30**: 611-613, 1956.

3. LAMBERT, C. R. — Nouveau traitement des schistosomiases et de l'amibiase, le Ciba 32,644-Ba. **Acta Trop. 23**: 1-80, 1966.

4. LAMBERT, C. R. & STAUFFER, P. — Chemotherapy of experimental **Schistosoma mansoni** infections with a nitrothiazole derivative, Ciba 32,644-Ba. **Ann. Trop. Med. Parasit. 58**: 292-303, 1964.

5. LÄMMLER, G. — Beiträge zur experimentellen Schistosomiasis. I — Mitteilung Untersuchungen zur Chemoprophylaxe der Bilharziose. **Z. Tropenmed. Parasit. 9**: 294-310, 1958.

6. LUTTERMOSER, G. W. — A method for detecting schistosomicidal activity based on response of **Schistosoma mansoni** infections in mice to Fuadin therapy. **J. Parasit. 38**: 32, 1952.

7. LUTTERMOSER, G. W.; BRUCE, J. I. & MC MULLEN, D. B. — The prophylactic and curative activity of 1-maleinyl-4-(3-chloro-4-methyl-phenyl)-piperazine (Hoechst S-688) in experimental schistosome infections. **Amer. J. Trop. Med. & Hyg. 9**: 39-45, 1960.

8. PELLEGRINO, J. & FARIA, J. — The oogram method for the screening of drugs in schistosomiasis mansoni. **Amer. J. Trop. Med. & Hyg. 14**: 363-369, 1965.

9. PELLEGRINO, J. & KATZ, N. — Experimental chemotherapy of schistosomiasis mansoni. **In Advances in Parasitology.** Vol. 6, ed. Ben Dawes. New York, Academic Press, 363-369, 1968.

10. PEREIRA, L. H.; PELLEGRINO, J. & MELLO, R. T. — Activity of known antischistosomal agents against early developing forms of **Schistosoma mansoni. J. Parasit. 61**: 249-252, 1975.

11. PEREIRA, L. H.; PELLEGRINO, J.; VALADARES, T. E.; MELLO, R. T. & COELHO, P. M. Z. — A new approach for screening prophylactic agents in schistosomiasis. **Rev. Inst. Med. trop. São Paulo 16**: 123-126, 1974.

12. SADUN, E. H.; BRUCE, J. I.; MOORE, J. W. & MC MULLEN, W. B. — The prophylactic and curative activity of a nitrothiazole derivative, 1-(5-nitro-2-thiazolyl)-2-imidazolidinone, in **Rhesus** monkeys experimentally infected with **Schistosoma mansoni** and mice infected with **S. japonicum. Acta Trop. (Suppl.) 9**: 69-77, 1966.

13. SCHUBERT, M. — Effect of drugs during earliest stages of experimental schistosomiasis mansoni in mice. **Amer. J. Trop. Med. 28**: 157-162, 1948.

14. STANDEN, O. D. — The progress of degenerative changes in schistosomes following the treatment of experimental infections with 1:7 - bis(p-dimethylamino-phenoxy) heptane. **Trans. Roy. Soc. Trop. Med. Hyg. 49**: 416-423, 1955a.

15. STANDEN, O. D. — The treatment of experimental schistosomiasis in mice: sexual maturity and drug response. **Ann. Trop. Med. Parasit. 49**: 183-192, 1955b.

16. STANDEN, O. D. — Drug activity against trematodes. **Second International Congress of Parasitology - Proceedings, Part 5**: 108-115, 1971.

17. STOHLER, H. R. & FREY, J. R. — Chemotherapy of experimental schistosomiasis mansoni: prophylactic and protective activity of clinically active compounds in mice and hamsters. **Ann. Trop. Med. Parasit. 57**: 466-480, 1963.

18. STOHLER, H. R. & FREY, J. R. — Chemotherapy of experimental schistosomiasis mansoni: prophylactic, protective and therapeutic activity of sodium antimony dimercaptosuccinate and antimony dimercaptosuccinic acid in mice and hamsters. **Ann. Trop. Med. Parasit. 58**: 280-291, 1964.

19. THOMPSON, P. E.; MEISENHELDER, J. E. & NAJARIAN, H. — Laboratory studies on the effects of tris (p-aminophenyl)-carbonium salts, tris (p-aminophenyl) methanol, and Lucanthone hydrochloride against **Schistosoma mansoni. Amer. J. Trop. Med. Hyg. 11**: 31-45, 1962.

20. YOKOGAWA, M.; YOSHIMURA, H. & SANO, M. — Experimental studies on the therapeutic effect of Ciba 32,644-Ba against **Schistosoma japonicum** in mice. **Acta Trop. (Suppl.) 9**: 78-88, 1966.

Recebido para publicação em 20/5/1975.