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Hycanthone in 1,035 Cases of Vesical Schistosomiasis

BY

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Rosi et al. (1965, 1967) and Berberian et al. (1967-a, 1967-b) described the preparation and experimental activity of hycanthone, a new schistosomicidal agent obtained by microbiological oxidation of lucanthone. Hycanthone is the 4-hidroxy-methyl-analogue of lucanthone and its chemical, physical and biological properties suggest that it is the active therapeutic metabolite of the main product. Since 1967 the drug has been utilized in many clinical trials in *S. mansoni* and *S. haematobium* infections. The following authors have published the results of their studies: In Brasil, Cunha and Cançado (1967), Katz, *et al.* (1967), Pellegrino, *et al.* (1967), and Figueiredo, *et al.* (1968); in Southern Africa, Clarke, *et al.* (1969), Barry (1970), Greenfield & du Toit (1970), Maritz (1970), Pitchford (1970), and Rubidge, *et al.* (1970); in East Africa, Rees *et al.* (1970).

The clinical trial described in the present paper was conducted in Limpopo Irrigation Scheme, Mozambique, (Portugese East Africa) where the Institute of Medical Research has maintained a campaign against schistosomiasis since 1964. The Limpopo Scheme is an agricultural area in which rice is the predominant crop. The area is irrigated by a dam on the Limpopo River and is drained by open channels, through which the water moves slowly in the irrigation period (October or November to March or April, corresponding roughly with the rainy season) and lies, as small pools of water during the dry season. Stagnant pools also collect in the borrow-pits formed by the excavation of the canals and the consolidation of their banks. Weeds suitable for snail colonies grow abundantly in the irrigation canals and borrow-pits and especially in the drainage canals. The Limpopo Scheme consists of 14 villages with a population of about 5 000 Europeans and 2 000 Africans. The area also contains scattered hamlets with a total population of about 24 000. Each house in the villages of the Scheme has a chlorinated water supply laid on, and has water-borne sewage on a septic tank system. Houses in the uncontrolled area surrounding the Scheme do not have these amenities. In the scheme the prevalence of schistosomiasis at the beginning of this trial was found to be 19 per cent. in Africans (155 males and 164 females infected in 817 males and 864 females examined) and 2,5 per cent. in Europeans (91 males and 20 females infected in 2 243 males and 2 167 females examined).

Materials and Methods

In this trial, 1 035 individuals infected with *S. haematobium,* 874 Africans and 161 Europeans were treated with hycanthone between August 1969 and September 1970. The patients were divided in four groups treated at different dates (Table — 1) and those found with schistosome viable eggs in the urine at the second

Table 1

HYCANTHONE — DATE OF TREATMENT

Groups	Treatments			
	1st	2nd	3rd	4th
1	19th Aug. '69	3rd Nov. '69		
2	1st Oct. '69	17th Dec. '69	4th Mar. '70	
3	17th Dec. '69	4th Mar. '70	12th May '70	17th July '70
4	4th Mar. '70	11th May '70	17th July '70	25th Sept. '70

month follow-up were retreated until the urine examination of all the patients was negative. The drug was administered in a single injection of 3 to 3,5 mg. for kg. body weight.

Laboratory examinations — the urine was examined before treatment and two months after treatment. Urine samples were allowed to stand in conical flasks for about half an hour after which time 15 ml. of urine was collected from the bottom of the flask and was centrifuged at 1 500 r.p.m. for 10 minutes. The sediment was then examined and counted for schistosome viable eggs. The urine examinations at two months after treatment were always made on two consecutive days.

Side effects provoked by the drug were studied in the first 1 000 patients. Follow-up at two months after the first treatment was possible in 1 001 of the 1 035 subjects treated; after the second treatment in 91 of 93; after the third treatment in 14 of 15; after the fourth treatment the two last patients were both controlled (see Table — 2).

RESULTS

Efficacy — as it can be seen in Table 2, the cure rates two months after treatment were as follows:

After the first treatment — 90 percent.; after the second treatment — 83 per cent., with a cumulative cure rate of 98 per cent.; after the third treatment — 79 per cent, with cumulative cure rate of 99 per cent.; after the fourth treatment — 100 per cent., with a cumulative cure rate of 99,5 per cent.

Side-effects — in order to minimize subjective effects, patients were all questioned by the same doctor. Of the 1 000 patients in whom side-effects were studied, 58.9 per cent. had no complaints of any symptoms; in these patients tolerance to the drug was considered "excellent" (See Table — 3). Tolerance was considered "good" in 20 per cent of the patients (mild symptoms on the day of treatment or the next day); "fair" in 15,9 per cent (mild or moderate symptoms on two or three days, including, a few cases of vomiting); "poor" in 5,2 per cent (more severe symptoms including frequent vomiting). Side effects observed on three days, including the

Table 3

TOLERANCE TO HYCANTHONE MESYLATE IN 1 000 PATIENTS

Excellent	58,9%
Good	20,0%
Fair	15,9%
Poor	5.2%

Table 2

EFFICACY OF HYCANTHONE MESYLATE* AGAINST *S. haematobium* IN MOCAMBIQUE (Limpopo Irrigation System). PATIENTS STILL POSITIVE TWO MONTHS AFTER TREATMENT WERE RETREATED DOSE: 3.0 mg./kg., I. M.

TREATMENT	NUMBER TREATED	TWO MONTHS FOLLOW-UP EXAMINATION						
		PRESENCE OF VIABLE OVA						
		NO. EXAMINED	POSITIVE		NEGATIVE		CUMULATIVE NEGATIVES	
			No.	%	No.	%	No.	%
1st	1035	1001	95	10	906	90	906/1001	90
2nd	93	91	15	17	76	83	982/999	98
3rd	15	14	3	21	11	79	993/998	99
4th	2	2	0	—	2	100	995/997	99.5

*ETRENOL®

NOTE: The following interval of two months was selected to minimize confusion from reinfection in presence of continuing exposure and transmission.

Table 4

SIDE EFFECTS OF HYCANTHONE MESYLATE IN 1 000 PATIENTS

Day	% Vomiting	% Tender (Inj. Site)	% Headache	% Abdominal pain	% Myalgia	% Nauseas	% Anorexia	% Vertigo
1st	15,4	8,6	8,4	7,8	5,9	2,7	1,4	0,2
2nd	7.8	6,7	3,4	1,7	3,0	2,9	1,0	0,1
3rd	0.1	1,4	—	0,1	0,3	0,3	0,2	—

day of treatment, are summarized in Table — 4. On the first day, 15,4 per cent. of the patients vomited, 8,6 per cent complained of tenderness at the injection site, 8,4 per cent had headache, 7,8 per cent. abdominal pain, 5,9 per cent myalgia, 2,7 per cent. nausea without vomiting, 1,4 per cent. anorexia and 0,2 per cent. vertigo. The frequency of symptoms decreased considerably on the second day and was very low on the third day. In no case was it considered necessary to hospitalize the patients.

DISCUSSION

The study of the effectiveness of hycanthone shows that treatment with a single dose of the drug (3-3,5 mg. per kg.) can effect the cure, in a very high percentage of patients with vesical schistosomiasis. In our experience, niridazol also gives very good results in the treatment of the disease but at least four days are needed for treatment and side effects are a little more frequent (Ruas & Franco, 1966 and Ruas, 1969). Considering that it is probable that some of the patients may have immature forms (schistosomules) in the circulation during the time of actual efficacy of hycanthone in *S. haematobium* treatment, it is reasonable to conclude that the infection is greater than it is suggested by the over-all rate of 90 per cent. obtained in this trial, after the first treatment. The follow-up interval of two months was selected to minimize confusion from reinfection in presence of continuing exposure and transmission. As it can be seen through the cumulative cure rates, resistance to the drug did not develop in patients who needed more than one treatment.

SUMMARY

1 — A total of 1 035 patients with vesical schistosomiasis were treated with hycanthone.

2 — The over-all cure rate in 1 001 patients, followed up two months after the first treatment, was 90 per cent. and the cumulative cure rate, after the fourth treatment, was 99,5 per cent.

3 — The compound was generally well tolerated; side effects were usually mild or moderate and hospitalization was not needed in any of the patients.

4 — The results of the trial indicate that hycanthone mesylate is highly effective in the treatment of *S. haematobium* infection and in view of the fact that it is administered in a single dose, we consider it the best drug, available at present, for the mass treatment of the disease.

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RESUMO

Descreve-se um ensaio clínico com o Hycanthone no qual foram tratados 1,035 casos de schistosomíase vesical. O ensaio foi realizado no Colonato do Limpopo, em Moçambique, onde o Instituto de Investigaçao Médica mantém uma campanha anti-bilhárzica desde 1964. Depois de uma descriçao sucinta do meio físicio e humano, refere-se a prevalência da bilharzíase existente no início do ensaio (19% nos Africanos e 2,5% nos Europeus).

O medicamento foi administrado numa injecçao ùnica, na dose de 3 a 3, 5 mg. por quilo de peso. Os doentes com ovos viáveis de *S. haematobium* na urina, dois meses após o tratamento, foram tratados de novo, até à cura parasitológica de todos os pacientes. As percentagens de cura foram as seguintes:

Após o 1o. tratamento — 90%; após o 2o. tratamento — 83%, com uma percentagem cumulativa de 98%; após o 3o. tratamento — 79%, com uma percentagem cumulativa de 99%; após o 4o. tratamento — 100%, com uma percentagem cumulativa de 99,5%.

No que respeita aos efeitos colaterais do medicamento verificou-se o seguinte: 58,9% dos doentes nao referiram queixas; 20% apresentaram sintomas ligeiros no dia do tratamento ou no seguinte; 15,9% apresentaram sintomas ligeiros ou moderados duran te 2 ou 3 dias incluíndo vómitos; 5,2% apresentaram sintomas mais severos, incluíndo vómitos frequentes.

No dia do tratamento 15,4% dos doentes tiveram vómitos, 8,6% queixaram-se de dor no local da injecçao, 8,4% tiveram cefaleias, 7,8% dores abdominais, 5,9% dores musculares e 2,7% naúseas. Os efeitos colaterias foram muito menos frequentes no 2o. dia e desapareceram pràticamente ao 3o. dia.

Nao foi necessário hospitalizar nenhum dos doentes tratados.

Pelos resultados obtidos e pelo facto de ser administrado em dose única, o Autor considera o Hycanthone como o melhor fármaco, disponível actualmente, para o tratamento em massa da Schistosomíase vesical.