Trials with Ambilhar (Ciba 32644-Ba) in the Treatment of Bilharziasis in Rhodesia

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Ambilhar has been selected as the trade name for the CIBA drug, previously known under the code number 32644-Ba, which was developed for use in the treatment of bilharziasis and amoebiasis. This drug has received considerable publicity and it has now been released in limited quantities for use in the treatment of bilharziasis in Rhodesia. The majority of the reports on trials with this drug have been published in "*Acta tropica*", a journal which is not readily available to medical practitioners in Rhodesia. It was therefore felt that a brief summary of the trials conducted in Rhodesia would be of interest.

Ambilhar is an organic compound with the chemical name 5-[nitrothiozolyl-(2)]-2-oxo-tetrahydro-imidazole, and it has no chemical similarity with any drugs previously used in the treatment of bilharziasis. However, it has some similarities with the nitrofurazole group of drugs which have been much used in the treatment of urinary bacterial infections.

Trials in Rhodesia

Over the past fourteen months three series of trials of this drug have been conducted in African communities in Rhodesia. In addition, a large number of individual cases, both European and African, have been treated on an experimental basis.

The first trial in February, 1965 in an African community living on an irrigation estate in the Lower Mazoe Valley, was reported by Blair and Clarke (1966). Seventy-four people of all ages and weights, each with heavy infections of both *Schistosoma haematobium* and *S. mansoni* were treated with Ambilhar at a dose level of 25 mg/kg daily in divided doses, morning and evening, for five days. An additional 19 people, also with double infections, were selected at random as a control group. Exhaustive follow-up examinations were conducted at 4, 8, 12 and 18 weeks after completion of treatment. The therapeutic effects of the drug were estimated by separating the results from individuals into five categories.

Category 1—no eggs.

2—only dead eggs, with great reduction in numbers.

3—few eggs; no active hatching, but miracidia showing activity in the unhatched eggs.

4—significant reduction in numbers of eggs, but miracidia still hatching.

5—little or no reduction in number of eggs. Miracidia still hatching.

Categories 1 and 2 are considered as "cures" after the 12 weeks' follow-up examination.

The results are presented in Table 1.

For *S. haematobium* infections 66/69 (96%) showed apparent cure, being in categories 1 or 2; and for *S. mansoni* infections 49/69 (71%) showed similar cures at 12 weeks after treatment.

The second two series of cases were treated in December, 1965 on a farm near Bindura in the Mazoe Valley. People of all ages were chosen, and they included persons with single or double infections. Intensive snail control measures were initiated in November, 1965, and they have been maintained throughout the period of the trial and follow-up examinations to reduce the possibility of re-infection. The cases were divided into two groups in which the types and intensities of infection of the cases were roughly comparable.

Table I

Chipoli Trial: February, 1965
(25 mg/kg daily, divided dose, five days).
Assessment of results at 12 weeks after treatment.

Category	*S. haematobium* in urine	*S. mansoni* in stool
1	36	3
2	30	46
3	3	8
4	—	3
5	—	9
TOTAL	69	69

In the one series 53 people were treated at a dosage level of 25 mg/kg daily for seven days, and in the other series 62 people were treated at the same daily dose for 10 days. In all cases the daily dose was divided into morning and afternoon doses.

The results are presented in Tables II and III.

Table II

Barassie Trial: December, 1965.
(25 mg/kg daily, divided dose, seven days).
Assessment of results at 12 weeks after treatment.

Category	*S. haematobium* in urine	*S. mansoni* in stool
1	20	16
2	4	3
3	—	—
4	—	4
5	—	11
TOTAL	24	34

It was unfortunate that many of the people treated in these two series failed to report for follow-up examinations at 12 weeks. However, all 24 *S. haematobium* infected people examined

Table III

Barassie Trial: December, 1965.
(25 mg/kg daily, divided dose, 10 days).
Assessment of results at 12 weeks after treatment.

Category	*S. haematobium* in urine	*S. mansoni* in stool
1	38	19
2	9	2
3	—	—
4	—	9
5	—	12
TOTAL	47	42

from the series receiving treatment over seven days and all the 47 *S. haematobium* infected people of the 10-day series fell in categories 1 or 2, giving a virtually total elimination of evidence of infections of this species. For *S. mansoni* infections 19/34 (56%) of the people treated for seven days, and, in the 10-day series, 21/42 (50%) showed apparent cure, being in categories 1 and 2.

In all three series, and in the results from individually treated people discussed below, emphasis has been placed on hatching of miracidia or viability of eggs as it is considered that this is a vital aspect in the assessment of cure. The finding of a few dead eggs in a specimen passed even three months after treatment is considered to be of no significance.

In the individually treated cases, a number of different dosage levels were employed for different periods of treatment. The results are presented in Table IV. An examination of this table gives the following indications:

1. *S. haematobium* infections are easily cured, even at low total doses.

2. The *S. mansoni* infections are satisfactorily treated in adults, but in small children the dose level of 25 mg/kg daily for seven days is insufficient.

Analysis of Results

The results of these trials are essentially similar to those reported from other countries of the world. At 25 mg/kg body weight results from all areas showed a very high therapeutic effect of Ambilhar on *S. haematobium* infections. However, some anomalies do exist in the results of *S. mansoni* infections; and it was also perplexing

Table IV

Individual Cases Followed up for at Least 12 Weeks After Treatment.

No.	Race: Eur. or African	Wt. in lbs.	Dose in mg/kg daily	Duration of treatment in days	Category	
					S. haematobium in urine	*S. mansoni* in stool
1	Afr.	72	45	3	1	4
2*	Eur.	66	42	4	1	—
3	Afr.	32	33	4	1	2
4	Eur.	98	30	5	1	—
5*	Afr.	170	30	5	—	1
6*	Eur.	35	25	4	1	—
7*	Eur.	45	25	4	1	—
8	Eur.	211	25	5	—	1
9	Afr.	131	25	5	1	—
10	Afr.	120	25	7	1	1
11	Eur.	51	25	7	—	4
12	Eur.	35	25	7	—	4
13	Eur.	32	25	7	—	4
14	Eur.	31	25	7	—	4
15	Eur.	132	25	7	—	1
16*	Eur.	165	20	5	—	1
17	Afr.	138	20	10	—	2
18	Afr.	156	20	10	1	—
19	Afr.	126	20	10	—	1

* Given a single daily dose. The remainder given the dose divided into morning and evening doses.

that, on gross analysis, the five-day course of treatment showed better results than the two longer courses of treatment. It was noticed, however, that in the individually treated patients the results for *S. mansoni* infections in small children were poor. The results from the three large series were then analysed in relation to weight of patients. Those people in categories one and two, 12 weeks after treatment, were accepted as "cures". The results are presented in Table V.

Table V

S. mansoni infections: Analysis of combined results of three series of trials at dosages of Ambilhar of 25 mg/kg daily for five, seven or 10 days. Relation between apparent cure and weights of persons treated.

Weight in lbs.	No. treated	No. cured	No. per cent. showing cure
20— 39	13	4	30.8
40— 59	39	17	43.6
60— 79	25	16	64.0
80— 99	15	9	60.0
100—119	28	23	82.1
120 and over	25	20	80.0
TOTAL	145	89	61.4

Only the combined figures for all three trials are given in the table since there were insufficient numbers in some of the age groups in the individual series. Despite this, the individual series showed similar trends with cures of *S. mansoni* infections above 70% in the adults of all series.

These results demonstrate that the therapeutic effect of Ambilhar at a dosage of 25 mg/kg daily for five, seven or 10 days is limited in small children and it is maximal in heavy adults. Since the report from other countries seldom include the weights of the patients treated, this factor could explain the differences in the reported results of treatment of *S. mansoni* infections. There are two possible explanations for this phenomenon, which could be acting simultaneously.

1. Newsome (1962) and other workers reported on the potentiation of therapeutic effect of lucanthone hydrochloride in animals which were showing partial resistance to schistosome infections. Since it is probable (Clarke, 1966) that the adults and older children in an endemic area are partially resistant to infections, this potentiation of drug effect could be acting in man. However, since European adults are unlikely to have developed resistance, and yet they respond in the same way, it must be the inadequacy of dosage which causes failure of treatment in small children.

2. The use of milligrams of drug to unit of body weight is an arbitrary basis for dosage since it is unlikely that the required dose to maintain an effective drug concentration in the circulation in a child is the same as it is in an adult.

It is probable therefore, that a graded dosage schedule in which the dose/weight ratio is loaded for small children will be required to achieve effective treatment of *S. mansoni* infections. It is the intention of the authors to conduct a trial in which children of weights up to 20 kg will receive a daily dose of 40 mg/kg of Ambilhar, but the dose will be graded down to a level of 30 mg/kg in adults of 50 kg or more. This dosage will be maintained for six days since it is considered that this is the maximum practical period for effective treatment under field conditions in Africa.

Side Effects

The series of patients treated on an individual basis were selected because they were controlled cases where it was possible to make detailed observations on tolerance or toxicity of the drug. This was not possible in the three large series where the treated people continued with their normal activities as farm labourers or families of the labourers.

The following reactions to the drug were observed:

1. The drug is very rapidly absorbed and metabolised, and because of this the urine assumes a strong yellow-brown colour and unpleasant musty odour. A similar mustiness has been reported as a general body odour in some patients. It is felt that patients should be warned of this since it can lead to alarm.

2. A common complaint was a general feeling of tiredness and sleepiness. It is possible that these complaints represented, in a very mild form, the effects of the drug, described as neurological effects, by other workers. These reports refer to effects leading to convulsions and other alarming but transient manifestations in people treated at high dose levels. In three cases in Rhodesia, all of one family (case numbers 12, 13 and 14 of Table IV), the patients woke from deep sleep at night, fainted momentarily, and then again slept deeply without further ill effect.

3. Some patients have reported mild nausea and occasional vomiting. These effects have almost invariably been limited to the first three days of treatment, usually in the early hours of the morning.

4. Some reports refer to inversion of T-wave in electrocardiographic investigations of treated people. This is described as temporary and of limited significance.

5. Some reports have referred to a temporary inhibition of spermatogenesis during treatment. In those laboratory animals and human cases in which this has been observed, the period of inhibition has been followed by an increase of sperm release after which the man returns to normal.

It must be emphasised that, generally, the side effects are very mild compared with those in patients receiving lucanthone or antimony drugs, and invariably those side effects which are noticed disappear on or even before completion of treatment.

CONCLUSIONS

In these early trials of Ambilhar this drug shows promise of being the most important advance in the chemotherapy of bilharziasis since the introduction of tartar emetic. It still remains to establish the optimal dosage levels for *S. mansoni* infections, and until these are established it is necessary to restrict the use of this drug to hospitalised patients. However, it is our opinion that Ambilhar, apart from being the most satisfactory drug available for the treatment for bilharziasis, will be used essentially for out-patient or mass treatment.

It is felt that it is of cardinal importance to establish an effective schedule for the treatment for *S. mansoni* infections, since, in an endemic area, it is difficult to exclude the possibility of a concurrent *S. mansoni* infection when *S. haematobium* has been established. In Rhodesia, at least, it is felt that all cases should be treated on a schedule which is effective against *S. mansoni* infections.

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