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Field Trial of Hycanthone (Etrenol Winthrop) in the Treatment of Urinary and Intestinal Bilharziasis

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Introduction

Treatment of bilharziasis with lucanthone hydrochloride has been well established for nearly 20 years. Its introduction represented a striking advance, as it was the first effective drug which could be taken orally. The length of the course of treatment by lucanthone hydrochloride of three to five days also represented a great advance over the antimonial drugs which, at that time, required much longer courses of treatment. For the first time a drug which offered hope as a mass chemotherapeutic agent had appeared.

Lucanthone hydrochloride was shown to be effective against *Schistosoma haematobium* infections on a three-day course of treatment, but was less effective against *S. mansoni* infections even when treatment was continued for five to seven days.

There seemed little possibility of improving therapeutic efficiency by increasing the daily dose intake above 20 mg./kg. of body weight, and even at this level patient tolerance of the drug in some parts of the world was poor.

Even in the most favourable circumstances there were many reports of unpleasant side effects. These toxic side effects were more severe and observed more frequently in adults than in children. In some endemic areas, however, even in children lucanthone hydrochloride produced such a high proportion of side effects that mass treatment of the disease was not considered to be a practical possibility.

Efforts were made over the years to try to reduce the incidence of side effects by administering lucanthone hydrochloride in combination with other drugs, e.g., belladonna and barbiturates, with the objective of alleviating the ill effects. Modification of the salts of lucanthone, e.g., lucanthone pamoate, and the dispensing of the hydrochloride salt in sugar and enteric-coated tablets were also tried, but these devices have not been proved to be of value in reducing toxicity. The rationale of the practice of administering adjuvant drugs rests on the belief that the side effects were due not only to the drug, but also, in part, to the death and decay of the worms in the body. The belief has persisted, and it is a common practice to prescribe these adjuvant drugs with any of the schistosomicidal drugs used in the treatment of bilharziasis. Although there may be some substance to this belief, it has been carried to extremes. In the case of lucanthone hydrochloride it is known that one metabolite is therapeutically effective, whereas the unmetabolised drug in the circulation accounts for most of the toxic side effects. Reduction in the concentration of unmetabolised drug in the circulation should therefore result in diminished side effects.

Hycanthone (Etrenol Winthrop)

Berberian *et al.* (1967a, 1967b) and Rosi *et al.* (1967) described the preparation and trial of hycanthone in experimental infections in animals. Microbiological oxidation of lucanthone furnished hycanthone, the 4-hydroxy-methyl-analogue of the main product. It was shown to be a highly active schistosomicidal agent when given orally or by intramuscular injection to animals. It has been identified chromatographically in the urine of man, monkey and mouse, following medication with lucanthone. Its chemical, physical and biological properties suggest that hycanthone is indeed the active therapeutic metabolite of lucanthone mentioned above. The drug is now under clinical trial in a number of endemic bilharziasis areas, and Katz and Pellegrino (1967) claim that approximately 80 per cent. of 52 patients with active *S. mansoni* infection were

deemed to be cured four months after treatment. The dose employed in this trial was 2-3 mg./kg./day for five consecutive days, the daily dose being administered orally.

The results in *S. haematobium* infected cases are reported to be even more encouraging. By mouth, the drug is administered in enteric-coated tablets containing hycanthone (Win 24, 933-2) and can be given in a single dose daily at 2.5 mg./kg./day for three or four days. It may also be administered intramuscularly as a *single* injection of 3 or 3.5 mg./kg.

The drug is reported to be very effective with the minimum of unpleasant side effects.

FIELD TRIALS IN RHODESIA

Following these encouraging results, it was decided to stage, in Rhodesia, a trial of hycanthone in the treatment of patients suffering from infections with *S. haematobium*, *S. mansoni* or with both parasites. The trial was undertaken on labourers and their families living on the farm Mayfield, situated approximately 20 miles north-west of Salisbury. In preparation for the trial, to reduce the possibilities of re-infection of patients, a snail survey was done on the farm and intensive snail control measures were introduced approximately six months prior to chemotherapy. The control depended on the regular application of Bayluscide (Bayer) and constant snail surveillance by the methods of Shiff and Clarke (1967).

Of the total of over 200 people who were tested, 97 were found to be infected with one or other or both species of schistosome. These were selected for the trial and they were divided, according to age, sex and type of infection, into four similar groups, as shown in Table I.

These four groups were given different dosage regimens as follows: Group A received 2.5 mg./kg./day single oral dose daily for three days; Group B received 2.5 mg./kg./day single oral dose daily for four days; Group C each received a single intramuscular injection of 3.0 mg./kg.; and Group D each received a single intramuscular injection of 3.5 mg./kg. In Groups C and D a maximum dose of 200 mg. per patient was imposed.

Treatment was commenced on 19th March, 1968, following a detailed pretreatment examination which included *S. haematobium* egg counts in the urine, *S. mansoni* egg estimations in the stool and hatching of miracidia from both stool and urine.

Similar examinations for post-treatment assessment were undertaken at approximately one, two, three and six months from the date of treatment on 23rd April, 21st May, 25th June and 20th September, 1968, respectively. All patients from all groups were examined daily during the four-day treatment period of Group B, and reports of side effects volunteered by the patients were recorded. In addition, retrospective questioning on side effects of each patient was undertaken one week after cessation of treatment.

RESULTS

The results of post-treatment examinations are summarised in Tables II, IIa and IIb. Table III gives a summary of the reported and observed side effects during the four-day treatment period.

It can be seen that the therapeutic efficacy of hycanthone compares satisfactorily with tha

Table I

DISTRIBUTION OF PATIENTS BY SEX, AGE AND WEIGHT

Group	SEX		AGE IN YEARS				WEIGHT IN LBS.					
	M.	F.	Under 10	10-20	21-40	Over 41	Under 44	45-65	66-87	88-109	110-131	132+
A	14	11	7	1	10	7	4	4	0	2	11	4
B	17	6	6	9	6	2	1	6	3	2	8	3
C	18	7	4	8	12	1	1	3	4	6	9	2
D	12	12	4	8	8	4	2	5	1	7	8	1
TOTAL	61	36	21	26	36	14	8	18	8	17	36	10

Table II

RESULTS OF POST-TREATMENT EXAMINATIONS OF BILHARZIASIS PATIENTS TREATED WITH HYCANTHONE

Dosage Group	*S. haematobium*						*S. mansoni*					
	No. Rx	No Viable Ova					No. Rx	No Viable Ova				
		1 Month		3 Months		6 Months		1 Month		3 Months		6 Months
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A Oral 2.5 mg./kg./d. x 3 days (25 pts.)	8	6/8	75	6/8	75	8/8	100	8	7/8	88	7/7	100	3/6	50
	9*	7/9	78	6/7	86	5/7	71	9*	8/9	89	6/7	86	7/7	100
	17	13/17	76	12/15	80	13/15	87	17	15/17	88	13/14	93	10/13	77
B Oral 2.5 mg./kg./d. x 4 days (23 pts.)	8	8/8	100	8/8	100	7/7	100	5	3/4	75	5/5	100	3/5	60
	10*	8/10	80	8/10	80	9/10	90	10*	8/10	80	8/10	80	5/10	50
	18	16/18	89	16/18	89	16/17	94	15	11/14	79	13/15	87	8/15	53
C I.M. 3.0 mg./kg. single dose (25 pts.)	9	8/9	89	8/9	89	6/8	75	7	6/7	86	4/6	67	5/6	83
	9*	9/9	100	9/9	100	9/9	100	9*	6/9	67	8/9	89	8/9	89
	18	17/18	94	17/18	94	15/17	88	16	12/16	75	12/15	80	13/15	87
D I.M. 3.5 mg./kg. single dose (24 pts.)	9	8/9	89	7/9	78	7/9	78	7	7/7	100	6/7	86	6/7	86
	8*	8/8	100	8/8	100	7/8	88	8*	6/8	75	6/8	75	5/8	63
	17	16/17	94	15/17	88	14/17	82	17	13/15	87	12/15	80	11/15	73

* Double infection.

Table IIa

SCHISTOSOMACIDAL ACTION OF HYCANTHONE AGAINST S. HAEMATOBIUM INFECTION

Group	No. Rx	RESULTS Patients Negative for Viable Ova at—							
		1 Month		2 Months		3 Months		6 Months	
		No.	%	No.	%	No.	%	No.	%
A Oral 2.5 mg./kg./d. x 3 days	17 (9)	13/17	76	14/17	82	12/15	80	13/15	87
B Oral 2.5 mg./kg./d. x 4 days	18 (10)	16/18	89	16/18	89	16/18	89	16/17	94
C I.M. 3.0 mg./kg. single dose	18 (9)	17/18	94	17/18	94	17/18	94	15/17	88
D I.M. 3.5 mg./kg. single dose	17 (8)	16/17	94	15/17	88	15/17	88	14/17	82

(n) = patients who were also infected with *S. mansoni*.

Table IIb

SCHISTOSOMACIDAL ACTION OF HYCANTHONE AGAINST S. MANSONI INFECTION

Group	No. Rx	RESULTS: Patients Negative for Viable Ova at— 1 Month No.	1 Month %	2 Months No.	2 Months %	3 Months No.	3 Months %	6 Months No.	6 Months %
A Oral 2.5 mg./kg./d. x 3 days	17 (9)	15/17	88	15/16	94	13/14	93	10/13	77
B Oral 2.5 mg./kg./d. x 4 days	15 (10)	11/14	79	11/15	73	13/15	87	8/15	53
C I.M. 3.0 mg./kg. single dose	16 (9)	12/16	75	11/15	73	12/15	80	13/15	87
D I.M. 3.5 mg./kg. single dose	17 (8)	13/15	87	11/15	73	12/15	80	11/15	73

(n) = patients who were also infected with *S. haematobium*.

of any other schistosomicidal drug tested under similar conditions.

Although it was not possible to draw firm conclusions because of insufficient people in each group, there appeared to be little difference in the therapeutic efficiency of the two dose levels of the oral medication. Similarly, there was little difference between the two dose levels of injectable drug as used in Groups C and D. However, the injectable material compared favourably with the oral, since the therapeutic activity was the same, but there were indications of fewer and milder side effects when using the injectable drug.

It was noticeable that the majority of patients who passed numbers of viable eggs at one month would be found to be passing eggs at all later examinations. Thus the failures were usually detected within the first two months after treatment. Of the 90 patients followed for six months after treatment, eight indicated relapse or re-infection at only the six-month follow-up examination. Since the snail control measures were restricted to the farm on which the patients lived, and since there is considerable intervisiting between farms, some or all of these were possible re-infections. However, for the assessment of th results these were classed as failures.

Within the groups treated there were te women who were subsequently proved to h pregnant at the time of the trial or who becam pregnant during the follow-up period. At th time of writing, six of these have delivered them selves of their babies. No mothers or babie showed any ill effect from the treatment.

Three patients, who on pre-treatment examina tion were only found to have *S. haematobiu* infection, were found, during post-treatmer examination, to have had concurrent *S. manso* infections. One of these passed hatchable *mansoni* eggs in the stool, whereas the other tw were only found to be passing dead eggs. The findings were not included in the assessment the results.

It is of interest to record that there were n complaints of pain, stiffness or any other loc side effect at the actual site of the injection hig up under the iliac crest in the gluteus minimu This was attributed to the very strict adheren to the manufacturers' recommendations to u this site for injection.

Table III

FREQUENCY OF OCCURRENCE OF SIDE EFFECTS

Group	Number Without Side Effects	Number Reporting Only Single Vomiting Episode	Number Reporting Additional Side Effects	Total
A	22	0	3	25
B	16	2	5	23
C	15	7	3	25
D	17	2	5	24

DETAILS OF ADDITIONAL SIDE EFFECTS

Group	Patient Number	Type of Infection	Vomiting Episodes	NUMBER OF REPORTS OF—				
				Headache	Anorexia	Abdominal Pain	Dizziness	Diarrhoea
A	24	Double	11	4	3	3	0	1
	2	,,	3	0	0	0	0	0
	41	,,	0	0	0	1	0	0
B	64	*mansoni*	0	0	4	0	0	0
	7	,,	0	0	1	1	0	0
	80	*haematobium*	0	0	0	0	4	0
	55	Double	0	0	0	2	0	0
	53	,,	2	0	0	0	0	0
C	77	Double	0	0	0	1	0	0
	84	,,	3	0	0	0	0	0
	20	,,	6	0	2	0	0	0
D	90	Double	0	0	0	1	0	0
	115	,,	3	0	0	0	0	0
	86	*mansoni*	3	0	0	0	0	0
	103	,,	2	0	0	0	0	0
	38	*haematobium*	0	0	0	1	0	1

CONCLUSIONS

Workers favouring mass chemotherapy of bilharziasis have long searched for a drug which would lend itself to this form of use. Lucanthone hydrochloride was found useful for the mass chemotherapy of *S. haematobium* infections and Ambilhar showed possibilities in the mass control of both *S. haematobium* and *S. mansoni* infections. However, both these drugs had disadvantages. With hycanthone, if the favourable initial trial results are maintained, a drug is available which is highly suitable for mass chemotherapy, having the following desirable characteristics:

(1) It is capable of administration by a single intramuscular injection—almost preferable to an oral administration, particularly an oral administration requiring three or more days of treatment.

(2) It achieves a satisfactory high cure rate on infections of both *S. mansoni* and *S. haematobium*.

(3) The toxicity, as observed in this admittedly limited trial, and as reported by other workers, is negligible.

If the manufacturers are able to market this drug at a cost which would allow its wide use, particularly in mass chemotherapy, then they will have achieved a great stride forward in the treatment and control of bilharziasis.

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