Clinical Trials of Hycanthone in the Treatment of Bilharziasis

BY

MICHAEL BARRY

Medical Service, Anglo American Corporation of South Africa Limited.

During the past few years, clinical trials of drugs in the treatment of bilharziasis have been carried out by medical officers of the Ernest Oppenheimer Mine Hospital at Welkom in the Orange Free State. The objective of these trials was not merely to assess their therapeutic efficiency, but also to assess these chemical agents in terms of the mass treatment of Bilharzia from the point of view of their ability to control the transmission of this disease. Side effects were also studied.

The Orange Free State Goldfield is a very suitable area for trials of this nature because it is a region that is free of bilharziasis, and therefore the problem of re-infestation does not arise in the assessment of the efficiency of anti-bilharzial drugs.

Several thousand men from regions where bilharziasis is endemic, enter the service of the mines of the Anglo American Corporation in the Orange Free State every year. Their homelands range from Malawi in the North to the Transkei in the South.

During the years 1961 and 1962 King and Foster[1] studied the efficacy of several drugs. Moreover a control group of 36 bilharzial patients, who did not receive treatment was also studied. It was found that the condition of the control group remained unchanged during a period of 9 months' observation, although there was some fluctuation in the number of ova that were present in the urine.

Amongst other investigations, the efficacy of Lucanthone and Win. 13820 was studied. Win 13820 is Becanthone which is an analogue of Lucanthone. As the result of their findings, King and Foster stated that provided the optimum dosage schedule of Becanthone could be found, it might well prove suitable for mass treatment because of its reliability and low toxicity.

In the meantime the Sterling-Winthrop Research Institute isolated the biologically active metabolite of Lucanthone, giving it the generic name of Hycanthone. It is a thioxanthone. This substance was originally isolated biologically but is now synthesised by a process of fermentation. In the chemical constitution of Lucanthone a methyl group is present. This radicle or 4 Methyl group is dissociated in the body and is changed to an hydroxy-methyl group. The Hydroxy-methyl group is the more active chemical in combating bilharziasis.

Further trials were then designed and performed and to determine the efficiency and tolerance of Hycanthone at various dosage levels. These trials were conducted during the period 1965-1967.[2] It became apparent from the results obtained here and at other centres such as Dennilton, Lourenco Marques and Salisbury that parenteral administration by the intra-muscular route was preferable to oral administration. The incidence of gastric side effects was considerably less when Hycanthone was administered by injection. It also became apparent that a single injection of Hycanthone could well be effective.

A further trial was therefore designed in 1968 to evaluate this probability. This work was accordingly commenced and is still being performed. The dosage was 3 mgs./Kg. body weight. The intramuscular route of administration was used and an aqueous solution of Hycanthone methanosulphonate was injected.

The absorption of Hycanthone from the deep intramuscular site reaches its maximum within half an hour of administration. It is almost completely excreted via the biliary system within 24 hours. Only very small amounts of Hycanthone are excreted via the kidneys.

The following is a report of the findings and conclusions of this trial.

Clinical Observations

Forty-two patients were observed clinically for the possibility of side effects.

Side effects were produced in 8 patients and were mild in most cases. Nausea was the most frequent side effect. Nausea occurred alone in 5 instances and did not occur until 4 hours had elapsed after administration of the injection. In one instance, it only appeared 13 hours afterwards. The duration of nausea in 2 cases was 4 hours. Nausea and vomiting occurred in 2 patients. One of these patients complained of abdominal pain but no abnormal clinical signs were observed on examination. The other patient vomited three times. In one instance pyrexia developed 2 days after the injection and was of 24 hours' duration. No cause was discovered for the pyrexia and it is possible that it was caused by Hycanthone. Jaundice was not observed nor did any patient complain of tenderness over his liver. No pain or discomfort was experienced at the injection site.

Table I

Side Effects.

Rate: 19 %
8/42.

Laboratory Investigations

Liver Function Tests

Serum transaminase, alkaline phosphatase and thymol turbidity estimations were performed prior to treatment and were then repeated 48-72 hours after injection.

Table II

Serum Transaminases:

S.G.O.T. and S.G.P.T. values were estimated in International Units (normal range 2-35 units).

S.G.O.T.

Number of Observations: 50.

	Before treatment	After treatment
Range	5 - 55	5 - 51
Average	11	17

Three values exceeded the normal range after treatment.

S.G.P.T.

Number of Observations: 50.

	Before treatment	After treatment
Range	4 - 17	4 - 60
Average	7.7	14

Two values were in excess of the normal range after treatment.

ALKALINE PHOSPHATASE.

Normal 3-13 Units.
Number of observations: 50.

	Before treatment	After treatment
Range	4.2 - 24.4	3.5 - 18.9
Average	7.8	7.6

Four values were in excess of the normal range after treatment.

THYMOL TURBIDITY.

Normal 0-2 Units.
Number of observations: 42.

	Before treatment	After treatment
Range	0.2 - 7	0.8 - 6.6
Average	1.5	1.9

The results of these liver function tests show that Hycanthone had minimal effects in a few instances.

Microscopic Examinations:

Specimens of urine were examined microscopically for the presence of viable ova of *Schistosoma haematobium* at intervals of 1 month, 3 months and 6 months, after treatment.

Absence of viable ova at follow up examinations was observed in the great majority of cases.

TABLE III.

Time	*Number of Patients*	*Absence of viable ova*
1 Month	24	22
3 Months	18	16
6-12 Months	11	11

The results of this trial were satisfactory. The toxicity of Hycanthone was minimal and a high rate of cure was observed.

CONCLUSIONS

Hycanthone methano-sulphonate can be administered as a single intra-muscular injection in urinary bilharziasis. Its efficacy is satisfactory and its toxicity is minimal.

This drug is therefore very suitable for mass chemotherapy as a means of bilharzia control, by eradicating the definitive hosts who are transmitters.

Hycanthone may well be the means towards a great advance in the control of bilharzia on a continental scale. Its impact in this sphere may prove to be comparable with the effect of D.D.T. on the control of malaria and penicillin in yaws.

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REFERENCES

1. KING, B.A. & FOSTER (1964). *S. Afr. Med. J.* **38**, 388.
2. POTGIETER, I., ZEILINGER, C. & HANSFORD, F. *Reports of Ernest Oppenheimer Hospital.*

DISCUSSION

Dr. Clarke, in reply to an unrecorded question concerning the importance of viable and non-viable ova, replied:

> I don't think this is the time to start on an argument on the importance of viable and non-viable eggs. The only method which will give any degree of accuracy is to differentiate between them. Perhaps, if there is time, Dr. Blair might give some indication of the results he is getting on some patients he treated up to 18 months ago. One patient (William) still passes batches of dead, calcified eggs on occasions, but he has passed no viable eggs.

Dr. Barry: I am talking about eggs with fully developed miracidia, ten weeks after treatment.

Dr. Blair: Does not the difference between Dr. Barry's and Dr. Pitchford's results depend on the area where they are working? Dr. Barry's region is not endemic for bilharziasis, and once he has killed the adults there are no more worms developing to take their place. Dr. Pitchford's eggs may come from adults developing at the time of treatment.

Dr. Pitchford: No, Mr. Chairman. Treatment was given at the end of the transmission season.

Dr. Almeida Franco: I would like to raise the question of SGOT and SGPT levels. These show a gradual rise after five to six days, and if you are measuring a rise after 48 hours, you ought to use some other test.

Dr. Barry: My experience is that you get a very rapid rise with these tests.

Dr. Shiff: I should like to ask Dr. Barry what he is looking for in these tests. If they just show dead tissue, could not the presence of dead worms cause a rise?

Dr. Barry: The transaminases rise as a result of damaged tissue. We are examining the blood itself and extraneous tissue, e.g., worms wouldn't affect it.

Dr. Elsdon-Dew: I think Dr. Shiff was trying to ask how much of the rise is due to dead tissue and how much to dead worms.

Dr. Barry: That I can't answer, not being a biologist, but what we are looking for is dead human tissue.