Oral Oxamniquine in the Treatment of Persistent Schistosoma Mansoni Bilharziasis

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Introduction

Oxamniquine is a drug which has been developed from the lucanthone series by Pfizer Limited of Sandwich, Kent, England. Foster and Richards (1969) have described the development of the drug which can be administered both orally and intra-muscularly. Clarke *et al* (1973) described trials of the intramuscular preparation in patients in Rhodesia, using this route with a single dose treatment. At the dose used (7,5 mg/kg of body weight) no cures were achieved, but there were indications that the drug had some effect both on *S. haematobium* and *S. mansoni* infections. The drug was remarkably free from toxic side-effects, but is caused a good deal of local pain at the site of the injection, and this pain persisted for some days.

Concurrently with these trials of the intramuscular preparation, initial trials were conducted using the oral preparation. The results

(unpublished data) showed a total absence of any side-effects, although at the dosages used, only slight indications of therapeutic activity were observed.

The lack of toxic side-effects reported in these earlier oral and intra-muscular trials showed that perhaps higher dose levels might achieve better results, and further trials (Clarke *et al.* in preparation) of the oral preparation showed very promising results, without significant side-effects at oral doses of up to 60 mg/kg given in divided doses over two days. With these results in mind, it was decided to use the drug to attempt to cure infections in three patients on whom repeated treatments had failed.

Trial in Three Patients with Persistent *S. mansoni* Infections.

These patients who had received repeated treatment for *S. mansoni* infections, were selected for treatment with oxamniquine.

(A) Patient L.M., an African male aged 22 years, has been under daily parasitological observation of his stool since March, 1971. Over the succeeding year until April 1972, he was treated on five occasions, with hycanthone, with niridazole, with niridazole and a very small dose of sodium antimony tartarate (SAT), with hycanthone, and also with a low dose of SAT with hycanthone. The *S. haemabotium* infection from which he was also suffering in March, 1970, was cured with the first hycanthone administered in April, 1972. The patient's stool still continued to show *S. mansoni* eggs, but the counts were reduced to a very low level compared with the pre-treatment level in March, 1974. Miracidia hatching from the daily stool specimen showed that this infection was still active after five treatments over the previous year.

At the time it was decided to continue the daily examination of the patient's stool with egg counts (Blair, *et al*, 1969) and miracidial hatching (Weber, 1973) to study the fate of the residual infection. However, it was then decided to try the new drug on this patient. At this time the average stool count was 100 eggs per week and miracidia were hatched from each daily specimen. On 27th July, 1972, he was given a single oral dose of Oxamniquine of 479 mg (8,6 mg/kg). This caused no toxic side-effects. Following treatment, the weekly egg counts were 60, 180, 240, 350, 70, 90 and 280 (weekly mean 180) and miracidia were hatched from all daily specimens except for one day in the fourth week. At 50 days after treatment no discernable curative effect was evident.

On the 19th September, 1972, the Oxamniquine treatment was repeated; this time he was given a single intra-muscular injection of 440 mg (8,0 mg/kg). He experienced considerable pain and stiffness, but there were no other side-effects from the drug administration.

Following this treatment, the weekly egg counts were 160, 110, 60, 190, 20 and 40 (weekly average 80), but miracidia were hatched throughout except for two of the daily specimens examined. The treatment was unsuccessful and the patient's daily egg counts and miracidial hatching soon returned to the levels observed before the first oral Oxamniquine treatment was given in July, 1972.

Daily stool egg counts and miracidia hatching were continued in the hope that the infection might die out spontaneously as the patient was not being exposed to the risk of further infection. Early in 1974 it became obvious from dose ranging trials in Rhodesia that the oral formulation of Oxamniquine was superior to the intra-muscular preparation and that a high dose/weight schedule was giving very encouraging results without an increase in toxic side-effects; it was therefore decided to treat the patient again on 13/14 March, 1974. For the two weeks prior to treatment the daily average egg count was 28 and on only one day were miracidia not hatched. The patient's weight was 55 kg and he was given 0,8 g of Oxamniquine morning and evening on two successive days, the total dose being 58 mg/kg. The daily examination of stool continued until 7th July, 1974.

The last egg seen was passed in the stool on 31st March, but the last occasion that miracidia were hatched was 26th March — five days earlier. The patient's weight was 55 kg in mid 1971, having risen to this level from 53 kg — his weight prior to his first treatment in March, 1971. When the follow-up studies were discontinued in early July, his weight had risen to 57 kg.

(B) Patient I.L., a male European aged 24 years, had no history of infection with bilharziasis prior to September, 1969. He was exposed to infection in late September and early October, 1969, and developed a classical Katayama syndrome along with many other cases reported by Clarke *et al,* 1970. Although feeling ill from about 20th October, he was not diagnosed as a case of *S. mansoni* infection until early December and received his first treatment with hycanthone on 30th December, 1969. Thereafter he was given repeat treat-

ments with the same drug at the same dose — 3 mg/kg — four times in 1970, four times in 1971, and the tenth treatment in March, 1972. Two months or more after each treatment examination of a series of stools showed low egg counts and miracidia hatched on most occasions. The patient spent a year in Britain working as a construction labourer and returned to Rhodesia in January, 1974. Three stool specimens revealed a light *S. mansoni* infection and miracidia were hatched in each case. As he had had a persistent but low grade infection for over four years it was decided to treat him with Oxamniquine, and this was done on 28th and 29th January, 1974. He was given 900 mg twice daily for two days, the total dose being 3,6 g (48 mg/kg). He reported slight abdominal pain on the afternoon of the first day of treatment, but no other side-effects. Six weeks later three stools taken on consecutive days were examined; no eggs were seen, but miracidia were observed in two of the specimens. His stools were re-examined two months later — three specimens showed no eggs and no miracidia were hatched. This was on the eve of playing rugby football for his country, and he looked and felt very fit indeed.

(C) Patient, J.T. A European male aged 34 years, contracted an acute *S. mansoni* infection with the classical Katayama syndrome, in the same locality as the previously described patient, but he was infected about one month later. His illness began on 3rd December, 1969, but *S. mansoni* eggs were not found in the stool until 5th January, 1970. The adult worm antigen skin test was negative, he had an eosinophil ratio of 39 per cent., an egg count of 200, and a moderately heavy miracidial hatch. During 1970 he was treated successively with hycanthone, niridazole, three hycanthone treatments at 2-3 months intervals, and finally in this year with three injections of hycanthone (each 3 mg/kg body weight), at weekly intervals. None of these treatments caused any side effects, and he continued in his strenuous and highly-skilled occupation. Re-examination of the patient and his stools was done during 1971 and early 1972. The patient was becoming worried about the possible effects of the infection on his occupation and it was agreed he would have a course of niridazole in February, 1972. Eggs were seen and miracidia hatched on each occasion he was re-examined, and further treatment was ruled out for the time being. In January, 1974, he reported again saying he was beginning to feel very tired and having some abdominal discomfort. Stool specimens showed he still had a residual *S. mansoni* infection and miracidia were hatched from the specimens.

On 14-15 February, 1974, he was treated with oral Oxamniquine — 950 mg twice a day on two successive days, a total dose of 3,8 g (49,3 mg/kg body weight). He experienced slight giddiness in the evenings of the two days of treatment. Follow-up examinations at eight and 10 weeks after treatment showed no eggs in the stool and no miracidia hatched. He now reported he was as fit and well as he was in 1969, and able to undertake long training runs to keep him in good shape for his very exacting occupation.

Discussion

We have insufficient evidence to show that where patients had failed to respond to treatment with hycanthone or niridazole, they would be cured with Oxamniquine.

Oxamniquine cured these three long-standing infections.

We are most impressed with the lack of side-effects from Oxamniquine in the three patients mentioned, and others, although we have had two patients at the time of writing, who had nausea.

All the other anti-schistosomicidal drugs attack the female worms but Oxamniquine attacks the male worm. This was observed from animal work done by Foster and Cheetham, 1973.

Summary

Three patients who had failed to be cured of their *S. mansoni* infections by other drugs, were cured by oral Oxamniquine.

Acknowledgements

We are grateful to Dr. V. de V. Clarke, M.L.M., Director of the Blair Research Laboratory, and Dr. E. Burnett-Smith, Secretary for Health, Rhodesia, for permission to submit this paper for publication.

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