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Urinary Bilharziasis: The Results of Treatment with Anthiomaline Administered Intravenously in Sixty-two Cases

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No agreement has yet been reached on a standard method of treatment of bilharziasis. The literature abounds with conflicting reports regarding the efficacy and safety of the various drugs used in bilharzial therapy, and many doctors must have difficulty in deciding which of these, including several new preparations, should be used. This study concerns the treatment of bilharziasis with intravenous anthiomaline. Treatment has been carried out under the best conditions, viz., in European patients who are unlikely to become reinfested and who have been found to be suffering from acute uncomplicated urinary bilharziasis. It was considered that under such conditions the drug and method used should never be dangerous and should produce few if any side effects. Further, it should be easy to administer and should have a high cure rate. Anthiomaline fulfilled all these criteria except possibly the last, and it was therefore decided to find out whether when given intravenously our previous poor results after intramuscular injection could be improved.

General Considerations

When Christopherson [1] clearly demonstrated the value of antimony it must have appeared that the problem of treatment, together with that of the life history of the schistosome, had finally been solved. It soon became apparent, however, that treatment with potassium or sodium antimony tartrate was not always effective and that there were many undesirable side effects and disadvantages. With this impetus chemists introduced alternative antimony compounds with the objects of ease of administration, minimum of toxic effect and high cure rate. The Germans produced fouadin and the French anthiomaline. Both drugs were soon extensively used, particularly in French North Africa, Egypt and South Africa.

More recently new trivalent antimony compounds such as sodium antimonyl gluconate have been introduced. In addition, working on entirely different lines, much research has been done on the use of oral substances such as lucanthone hydrochloride (miracil D) in the treatment of *S. haematobium* infection.

The modern management of schistosomiasis has recently been reviewed by Gelfand.[2] He considers that the following factors should govern the selection of a particular drug: age, sex, race, the stage of the disease, the patient's environment as regards the possibility of reinfection, whether a single patient is treated or whether a mass treatment is to be undertaken, and finally, the type of schistosome encountered.

It is generally accepted [3] that *S. mansoni* is more difficult to kill than *S. haematobium*, and that for its treatment large doses of antimony tartrate—up to 50 gr.—may be required. This has been borne out in our experience. Unfortunately we have only treated a small number of patients infested wth *S. mansoni* by intravenous anthiomaline and cannot therefore reach any definite conclusions. We have, however, had some failures with this form of treatment, and it is now therefore also our opinion that in the absence of contra-indications, cases of *S. mansoni* should be treated with large doses of sodium antimony tartrate.

Gelfand [2] also stresses the lack of unanimity on the vexed problem as to what constitutes a cure, and he suggests two criteria, viz., the disappearance of clinical symptoms and the permanent absence of ova (dead or alive) from the excreta six weeks after completion of treatment. Following our experience in Salisbury, these criteria appear to be inadequate. The first cannot be applied to the many symptom-free patients in whom ova are found in a routine

medical examination. In others, symptoms are vague, there may be no weight loss, no localising symptoms, and haematuria even if observed is usually transient despite no treatment. The time limit of six weeks, the second criterion, is probably too soon to prove a definite cure. This is well borne out in the investigations of Rodrigues Molina *et al.*,[4] who followed up 30 patients suffering from *S. mansoni* infestation after treatment with intramuscular anthiomaline. All had negative results at the completion of treatment: one was positive again at the fourth month; one at the eighth month; two at the eleventh month; two at the twelfth month; three at the fourteenth; four at the fifteenth; five at the sixteenth, and two at the seventeenth, giving a total of 20 relapses out of 30. Though the authors state that none of these patients gave a history of reinfection following treatment, this possibility always poses a difficulty when the patient remains in an infected area.

The reasons for this late relapse are not definitely known, but have recently been clarified following the treatment of infected experimental animals. Schubert[5] has shown in experimental bilharziasis in mice that the effects of antimonial drugs on the schistosomes (*S. mansoni*) are as follows: the worms become unpaired, leave their usual position in the terminal mesenteric vessels and migrate to the larger portal canals and to the liver. He also showed that after treatment the parasites would return to the mesenteric veins, copulate again, lay eggs and these would again be present in the faeces. It is very probable that a similar sequence of events occurs in man and that therefore frequent follow-up studies should be performed to exclude the possibility of relapse.

A further problem not yet settled is the significance of dead or non-viable ova. Many workers regard the presence of these ova as indications of the elimination of the worm; others again are equally emphatic that these ova do not necessarily imply the death of the worms. Whilst investigating the results of intensive antimony treatment, Girgis and Aziz[6] observed dead ova following this treatment, but they noted "a gradual change in the type of ova that were being passed, and by the end of the eighth week we found living ova in the urine of four patients." They continue that "it seems inconceivable that ova deposited in the wall of the bladder or rectum before treatment could take as long as a year to pass into the urine or stools, and we are inclined to believe that the dead ova found in some cases after treatment are produced by live schistosome worms in the patient. Some of these worms needed eight weeks to recover, but others may take much longer." Gelfand[2] also believes that dead ova do not necessarily indicate a cure.

In testing the efficacy of intravenous anthiomaline in *S. haematobium* infestations we decided to base our test of cure on the complete absence of ova in the urine three, six and twelve months after the completion of the course of treatment.

MATERIAL AND METHOD

The Patients.—All the patients were Europeans seen in private practice. All those who received intravenous anthiomaline during the period March, 1954, to September, 1955, are included in this investigation. A total number of 91 cases were treated, of whom 62 were male and 29 female. There were two children under the age of five years; 38 from 6-10 years; 40 from 11-20 years, and 11 over the age of 20 years. The patients were residents of Salisbury who had on one or more occasions swum in a pool or river in the surrounding neighbourhood.

Diagnosis.—The diagnosis of bilharziasis was only made when ova of *S. haematobium* were found in the urine. Though often suspected on clinical evidence and raised eosinophil counts, ova were as frequently found on routine investigation. This applied particularly to the cases detected in the schools check-up conducted by the Public Health Department. Most of the latter were completely symptomless.

When the disease was strongly suspected and in the case of all follow-up studies the patients were asked to supply an 8 oz. residue of a 24-hour urine specimen. This residue was centrifuged and the deposit examined. The entire sediment was poured on to a slide, a coverslip applied and the whole field systematically examined.

The Drug.—Anthiomaline is supplied in the form of a 6 per cent. solution and the multi-dose containers of 25 ml. were used. The drug (lithium antimony thiomalate) is a tri-valent organic compound containing 16 per cent. antimony. One ml. anthiomaline therefore contains .01 gm. antimony; 10 ml. .1 gm. and 50 ml. an average total dose, therefore, 0.5 gm. This can be compared to the antimony content of 0.7 gm. in 30 gr. of sodium antimony tartrate. Finally, in order to correlate the two drugs, an average single dose of 3 ml. anthiomaline contains approximately ½ gr. antimony, whereas an average single dose of 2 gr. sodium antimony tartrate contains approximately ¾ gr. of the metal.

The Method.—Following the demonstration of ova treatment with intravenous anthiomaline was started. The injections were given on alternate days, excluding Sundays. The first dose in all patients was 0.5 ml. The second dose was 1 ml. and the third and following doses were 2 ml. in children under the age of 10 years and 2.5 to 3.0 ml. for those over that age. The final dosage depended on the patients' reactions, but none was given more than 3 ml.

A total dose was 40-45 ml. for children under the age of 15 years and 45-55 ml. for adults. Here there was again some individual variation, depending mainly on body weight.

The injections were given slowly and the patient was told to rest for five minutes after its completion and to report any side effects at the following visit. Following the completion of the course, the patient was instructed to send an 8 oz. residue of a 24-hour specimen of urine three, six and twelve months later.

Results

Although a total number of 91 patients were treated, only 62 co-operated in follow-up studies. The results will therefore be limited to these 62 patients. In this group a total of 109 urine tests were done: 46 three months after completion of the course, 19 six months later, and 44 a year or more later. Every patient included had at least one follow-up test. No schistosome ova (alive or dead) were found in any of these tests.

Toxic Effects.—(1) *Coughing* occurred in a few patients soon after the injection was given. If excessive amounts are given coughing can be severe, but in the dosage used in this series this symptom was never troublesome.

(2) *Vomiting* caused by antimony is usually associated with severe spasms of coughing. In this series a few patients reported that they had vomited one to two hours after the injections. Only three vomited at the time of treatment. In two of these, both children, reduction of the dosage to 1 ml. produced similar effects and a change was made to intra-muscular injections. In one, a boy aged six years, alarming symptoms developed soon after this intra-muscular injection. He broke out into a profuse sweat, coughed and vomited almost continuously, his pulse became thready, his colour ashen grey and he appeared to be dying. During the following hour he gradually improved. Treatment was discontinued and, as he had already received 30 ml., the urine was repeatedly examined and showed no ova.

(3) *Muscle and Joint Pains.*—A certain amount of muscle and joint stiffness aggravated on the day following the injection was observed fairly frequently. Strangely this symptom has not been observed in children. The degree of stiffness and pain was far less than that seen during antimony tartrate treatment.

(4) *Herpes Zoster.*—One case of herpes zoster affecting the thigh area was observed in a nine-year-old female soon after the completion of the course. Recovery was complete after 10 days. The incidence of herpes zoster is very much lower than after antimony tartrate, particularly when the latter is given in the rapid form of treatment.[7]

(5) *Conjunctival Congestion.*—A mild conjunctival congestion coming on about in the middle of the course of treatment was seen in a few cases, mainly in children.

(6) Dermatitis, jaundice, dizziness, epigastric pain, pyrexia and other reported toxic effects were not seen.

Discussion

Anthiomaline was first used in the treatment of bilharziasis in 1936 and the first trials were made in French North Africa. Marchat and Couzi[8] treated soldiers infected with urinary bilharziasis with nine injections of anthiomaline and claimed good results. In the same year Moulinard[9] claimed that anthiomaline is a better drug against urinary schistosomiasis than either emetine or tartar emetic. He treated eight cases with each of these drugs. The daily and total doses given to boys aged 12-14 years were as follows: emetine 0.04 and 0.6 gm.; tartar emetic 0.08 and 1.2 gm.; anthiomaline 0.12 and 1.38 gm. Percentage cure rates at the end of treatment and some months later were: emetine 62.5 and 12.5; tartar emetic 75 and 25.0; anthiomaline 100 and 85.7. He commented further that there was no local or general reaction to anthiomaline and that there were no apparent contraindications to its use. In a similar experiment using stibenyl, tartar emetic, fouadin and anthiomaline, Richet[10] concluded that fouadin and anthiomaline were the most active and best tolerated drugs. In the treatment of children, Farges[11] found anthiomaline superior to tartar emetic. Further good results were reported by Panayatotou[12] and Pieri and Sardon.[13] Gobert[14] gave 3 ml. intramuscularly in adults for 11-13 injections. Twenty-six out of 44 patients were found to be cured after 3-4 months. He noted dizziness, nausea and vomiting in some cases and advised a two hours' rest after each injection.

In South Africa, Cawston[15] was early to use this new drug and wrote in 1936 of the advantages of anthiomaline treatment. He recommended that the first doses should be 0.5 ml. for a child of 12 and 1.5 ml. for the others, and that the repeated adult dose should not be more than 4 ml. He stated that he had obtained cures with less than 0.5 gm. (7½ gr.) antimony (i.e., 50 ml.). Later in the same year,[16] however, he concluded that "intravenous injections of potassium antimony tartrate in non-toxic doses is still the method of choice for urinary bilharziasis." He complained that the introduction of new remedies which could be administered with less skill had resulted in many treatment failures, and suggested that investigations should be carried out on an adequate number of cases to determine the total dosage necessary and the results obtained. In the cases treated by anthiomaline which Cawston then describes it is obvious that the dosage had been very inadequate. In some, however, the reports so truly reflect our experience with this drug that it may be interesting to quote one:—

"S.M., aged 21, with six years' history of infection with *S. haematobium*, was unsuccessfully treated a year ago with intramuscular injections (anthiomaline); complained of haematuria and three motions of the bowels daily. He was given ⅛ grain of tartar emetic, but, as he could not attend more than about once a week, intravenous injections of from 1¾ to 3½ ml. anthiomaline were given. No ova were found in repeated examinations of the urine after the 21st day, when he had received 23¼ ml. He was given a total of 39¼ ml."

He also reported failures when smaller amounts of anthiomaline were given, usually

intramuscularly. These failures must have influenced Cawston in reaching the conclusion noted above. It is unfortunate that to the authors' knowledge no large series of cases were reported in Southern Africa which were treated with adequate doses of intravenous anthiomaline and the drug was thereafter mainly used, intramuscularly, in children in whom intravenous therapy with antimony tartrate proved too hazardous.

In Egypt, Ashkar [17] reported on the use of anthiomaline in 24 patients with urinary schistosomiasis. Starting with 1 ml., he then gave 3 ml. and continued with 4.25 ml. Live ova ceased after dosages varying from 21.5 to 55.5 ml., but he observed many toxic symptoms, viz., abdominal pain, vomiting and headache. Gorsee and Accart [18] studied 65 recently infested European patients and 147 Africans in Morocco. They used three preparations: tartar emetic, fouadin and anthiomaline and judged the effects by repeated cystoscopic examinations. Anthiomaline proved to be the best drug, but in eight cases so treated there were four relapses some months later. Where fouadin was given in 11 cases there were no cures, and late results with antimony tartrate were also poor.

Aware of the new method of intensive treatment with antimony tartrate introduced by Alves,[19] Mills [20] working in a military hospital in West Africa decided in 1946 to try a rapid course of treatment using fouadin and anthiomaline. The principle of dosage was to give a maximum dose of antimony (nearly 0.5 gm.) in less than a fortnight. A course of anthiomaline consisted of daily injections (Sundays excepted) of 4 ml. intra-muscularly for a fortnight. Treatment was carried out in hospital, and during the second week patients were encouraged to stay in bed. Cystoscopy was performed before treatments, a week after the last injection and thereafter three times at monthly intervals. Toxic effects were noted in a total of five patients out of 46—the author does not state whether they were caused by anthiomaline or fouadin—and these were very mild, viz., vomiting and irritating coughs. A few others appeared listless towards the end of treatment. Of 26 cases, many of whom had massive infections treated by anthiomaline, only three were not cured by cystoscopic criteria. The author concludes that anthiomaline (and fouadin), when given in this concentrated method, will cure most cases of vesical bilharziasis.

Anthiomaline has also been used against *S. mansoni*, mainly in South America. As mentioned earlier, Rodrigues-Molina *et al.*[4] found the drug to be most effective when judged by immediate results, but on carrying out follow-up studies noted a very high relapse rate. Hernandez Morales *et al.*[21] also had excellent immediate results with *S. mansoni*. Both groups used anthiomaline intramuscularly in doses of 3 ml. to a total dosage of 30-45 ml. They report very few toxic manifestations, including slight pyrexia, conjunctival congestion, mild muscular and joint pains and, very occasionally, albuminuria.

In two recent cases of *S. mansoni* infestation, both young children, which we treated with intravenous anthiomaline, both with two courses, viable ova were still found in one six weeks after the completion of treatment. The failed case cleared following the use of sodium antimony tartrate.

The results obtained in the present investigation in cases of urinary bilharziasis are obviously excellent. It should, however, be stressed that the patients treated in this series were probably only lightly infested. Our patients had usually swum only infrequently in infested water. This is to be compared with the series of cases reported by Mills,[20] in which he found extremely severe infestations with numerous tubercles, ulcers and massive granulations on cystoscopy. Comparisons should therefore only be drawn between this course and other types of treatment in similarly infected groups. It would be interesting to find out whether intravenous anthiomaline would cure the heavily infested African who may wash daily for years in infested water.

Our interest in anthiomaline arose because of our dissatisfaction with the standard method of treatment of bilharziasis, viz., sodium antimony tartrate. Toxic effects were common and, particularly in children, the frequency of coughing, vomiting and marked prostration rendered the course a harrowing experience for both patient and doctor. The intensive treatment had also been tried, but this we considered too toxic and dangerous for routine use. In 1949 one of us (E.S.) treated a large number of school children with intravenous anthiomaline with a high cure rate, and this method was then continued.

The injections are almost painless and side effects have been minimal. If any anthiomaline is deposited outside the vein the patient only complains of a burning pain which soon disappears. We have not observed any painful swellings or abscesses in such cases. The freedom from side effects such as persistent vomiting

and coughing, tightness of the chest and local pain—all reactions which alarm the child—are most important in the treatment of children, who soon learn to overcome their fear of the injections. The only disadvantage of this course lies in the number of injections necessary, viz., about 20 in young children and 18 in adults.

Summary

(1) Ninety-one patients suffering from urinary bilharziasis were treated with intravenous anthiomaline. One hundred and nine specimens of urine from 62 of these patients were re-tested after the completion of treatment—46 three months later, 19 six months later and 44 a year later. No schistosome ova (alive or dead) were found in any of these tests.

(2) Toxic effects were very infrequent, but included coughing, vomiting, conjunctival congestion, stiffness of the muscles and joints and herpes zoster. In only three cases were these effects severe.

(3) The literature on the use of anthiomaline in the treatment of bilharziasis has been reviewed.

(4) Stress has been laid on the value of anthiomaline when, given *intravenously* in adequate dosage, it has proved the best method in our experience.

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