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The Effects of Drugs on *Onchocerca volvulus*

4. Trials of Melarsonyl Potassium*

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The effects of the arsenical drug melarsonyl potassium on Onchocerca volvulus *were investigated in patients in Cameroon infected with the Cameroon forest and Sudan savanna strains of the parasite. Two intramuscular dosage schedules were tested: the first comprised 4 consecutive daily doses of 200 mg repeated once after a 10–14 day interval, i.e., 2 (4×200 mg). The second was a single dose schedule at 7.1 mg/kg–10 mg/kg, with a maximum of 500 mg.*

In most trials the drug had no immediate action on microfilarial concentrations. Only after the 2(4×200 mg) melarsonyl course against the Sudan savanna strain was a slight microfilaricidal action detected.

The 2(4×200 mg) course of melarsonyl apparently killed or sterilized most or all of the adult female worms in the patients tested, leaving the residual population of microfilariae to decline gradually, from natural mortality, over the ensuing 2 years. These residual microfilariae could be killed with diethylcarbamazine.

Single doses of melarsonyl at 7.1 mg/kg–10 mg/kg were somewhat less effective in killing or sterilizing adult worms, but it is suggested that if doses at the higher end of this range were to be repeated annually patients could be rendered free from microfilariae by the end of 3 years.

It is emphasized that the risks of arsenical encephalopathy should at present preclude the use of melarsonyl potassium in the treatment of onchocerciasis, but that if this danger could be avoided the drug might prove to be of considerable use for mass therapy in control campaigns.

The organic arsenical melarsonyl potassium (Mel W) was developed by Dr E. A. H. Friedheim as a water-soluble derivative of melarsoprol (Mel B) suitable for intramuscular injection. It shows a relatively low degree of toxicity in small animals: the intravenous LD_{50} in mice was 105 mg/kg and this indicates a toxicity 3 times less than that of melarsoprol.

The drug has been reported to have a lethal or sterilizing action on the adult female worms of *Onchocerca volvulus*, but published opinions as to its efficacy vary. Friedheim (1962) tested 2 consecutive courses of 4 daily doses of 200 mg of melarsonyl in patients with onchocerciasis who were living in a leprosy settlement. Microfilarial densities were greatly reduced 20 months after treatment and, with the exception of a few males, all the adult worms examined were dead. Friedheim (1964) reported on 2 patients (treated and followed up in Cameroon and referred to in previous papers by Duke (1968a, 1968b, 1968c) in whom the drug undoubtedly destroyed the adult worms but had little direct effect on the microfilariae, some of which survived for more than 2 years after treatment.

From Upper Volta, Lartigue (1964) reported that in patients examined 10 months after receiving a single dose of melarsonyl at 7.5 mg/kg most adult *O. volvulus* were dead. Darrigol[2] found that only 21% of qualitative skin biopsies were negative 12 months after single doses of 6.7 mg/kg–10 mg/kg of melarsonyl, but examination of nodules excised at this time showed that a large proportion of the adult worms were dead. The action of the drug on adult

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[2] Darrigol, J. (1966) *Traitement de l'onchocercose par le Mel W. Résultats un an après injection unique.* In: *Rapport final de la Sixième Conférence Technique de l'OCCGE, Bobo Dioulasso*, vol. 1, p. 207 (unpublished mimeographed document).

worms was thought to be more rapid with higher doses.

On the other hand Lagraulet et al. (1966), working also in Upper Volta, treated patients with single doses of 7.5 mg/kg of melarsonyl (maximum 500 mg) and followed them over 22 months by examination of skin snips and excised nodules. They found no striking difference between treated groups and controls with regard to the parasitological effects of treatment, and although no quantitative assessment of the action on microfilariae was made, they concluded that the drug was not particularly effective. It should be noted that the onchocerciasis zones in Upper Volta lie in an area where a Sudan-savanna type of onchocerciasis occurs and that, as is usually inevitable on such trials, there was no control of transmission to prevent reinfections.

On the basis of the results obtained by Lartigue (1964) and Darrigol [1] which indicated that the drug might provide an effective, non-toxic, single-dose, intramuscular, macrofilaricidal treatment against *O. volvulus*, a large-scale field trial involving the treatment of 20 000 onchocerciasis patients with single doses of melarsonyl at 10 mg/kg was proposed by the Organisation de Coordination at de Coopération pour la Lutte contre les Grandes Endémies (OCCGE) in West Africa. However, about the time that this campaign was due to start, alarming reports of deaths from arsenical encephalopathy associated with melarsonyl therapy began to appear. Some of these have been summarized by Richet,[2] who quoted 1 death from encephalopathy out of 3247 patients treated with melarsonyl at 10 mg/kg for *Dracunculus* infection, and also 5 encephalopathies (4 fatal) out of 389 patients treated with 4 mg/kg – 5 mg/kg melarsonyl for *W. bancrofti* infection in French Oceania. Duke (1966) also reported a fatality from presumed arsenical encephalopathy in a patient who had received 7 doses of 200 mg of melarsonyl for treatment of *O. volvulus* infection; and Dr R. Davin (personal communication) encountered 5 non-fatal encephalopathies in a series of about 200 onchocerciasis patients treated at 7.5 mg/kg–10 mg/kg of melarsonyl at Edea, Cameroon.

On the strength of these reports the OCCGE campaign was initiated with great caution. The dosage of melarsonyl was reduced from 10 mg/kg to 7.5 mg/kg and large supplies of British anti-lewisite were made available to combat possible encephalopathies. Despite these precautions 4 fatal encephalopathies ensued in the first 4287 patients treated and the campaign had to be abandoned. Subsequently 1 further onchocerciasis patient treated in Upper Volta died from encephalopathy after a single dose of 6 mg/kg (Richet [2]). Since then, and quite correctly, there has been a general reluctance to use melarsonyl in the treatment of a non-fatal disease such as onchocerciasis, but some workers have persisted in testing single 315 mg doses in conjunction with an antihistamine in an attempt to control the toxic manifestations of the drug (Rives, Bernard & Kpan [3]).

The patients described in the present paper were all treated with melarsonyl before the catastrophe described by Duke (1966), and since then the author has not employed the drug further. However, in a series of trials of melarsonyl carried out from 1962 to 1966, including follow-ups made subsequently, a considerable amount of useful information has come to light on the potentialities of the drug, which is unique in being almost exclusively macrofilaricidal. The results are presented here for 2 reasons. Firstly, they demonstrate the potentialities and mode of use of a pure macrofilaricide in the treatment and control of onchocerciasis, i.e., principles that are likely to be applicable to any drug with similar properties that may be discovered in the future. Secondly, it may be that future research will reveal ways of avoiding the dangers of encephalopathy associated with melarsonyl, in which case the information provided here may have immediate practical application in the control of *O. volvulus* transmission.

MATERIALS AND METHODS

Patients included in the trials and examinations carried out

The patients treated were adult male Africans between the ages of 18 and 45 years and they were apparently in good health. They were treated in their villages where, in the absence of any *Similium* control, they were continually exposed to the risk of

[1] Darrigol, J. (1966) *Traitement de l'onchocercose par le Mel W. Résultats un an après injection unique.* In: *Rapport final de la Sixième Conférence Technique de l'OCCGE, Bobo Dioulasso*, vol. 1, p. 207 (unpublished mimeographed document).

[2] Richet, P. (1967) *La thérapeutique de l'onchocercose dans les Etats membres de l'OCCGE.* In: *Rapport final de la Septième Conférence Technique de l'OCCGE, Bobo Dioulasso*, vol. 1, p. 215 (Unpublished mimeographed document).

[3] Rives, M. Bernard, P. & Kpan, P. (1968) *Traitement de l'onchocercose par l'association Mel W (Trimelarsan)–diéthylcarbamazine (Notézine)* (unpublished document WHO/ONCHO/WP/68.26).

reinfection. Most were infected with the Cameroon forest strain of *O. volvulus* (Duke et al., 1966) and were natives of the Bolo-Weme-Baduma village complex, where the transmission of *O. volvulus* is known to be very heavy (Duke, 1968c), or of the villages of Bombe, Mundame and Bombele, where transmission is thought to be moderately heavy. Two groups of patients were infected with the Cameroon Sudan-savanna strain of *O. volvulus*, coming from the villages of Voko and Djelopo and their environs in the north of Cameroon. The intensity of transmission in these Sudan savanna villages is not known but it was probably greater at Voko than at Djelopo. It was considered desirable to make comparative investigations in forest and in Sudan savanna to determine whether the different strains of parasite, or the other environmental factors affecting the disease, might influence the results in any way.

Each patient was examined before treatment by taking 4 weighed skin snips, one from each buttock and calf, and counting the total numbers of microfilariae per mg of skin (Duke, 1968a). Re-examinations were made in a similar manner at various intervals up to 3 years after treatment.

Techniques of melarsonyl treatment and dosage schedules

The melarsonyl used was Trimelarsan (Specia, Paris) and was supplied as a white water-soluble powder in phials containing 200 mg. The powder was dissolved in sterile, pyrogen-free distilled water and was given by intramuscular injection into the deltoid, vastus externus or gluteal muscles.

Two different treatment schedules were investigated. The first was a multiple-dose schedule comprising daily injections of 200 mg of melarsonyl for 4 consecutive days, this course being repeated once after an interval of 10–14 days. This is referred to as the 2(4×200 mg) melarsonyl course; each dose of the drug was dissolved in 3 ml of water. The second schedule comprised a single-dose treatment of between 7.5 mg/kg and 10 mg/kg with a maximum dose of 500 mg. On this course, each 100 mg of the drug was dissolved in 1 ml of water making the maximum volume of the injection 5 ml.

In general, treatment was very well tolerated. Pain at the injection site lasting for 2–3 days was almost universal. It was most severe following the single-dose treatment in which a large volume of the dissolved drug was given. Out of 122 patients treated, 7 complained of severe pruritus all over the body lasting for 24 h–48 h after the single-dose treatment. Among the patients on the multiple-dose course, 3 developed severe pain, deep in the region of the hip joint, with temporary limitation of movement. One patient (not recorded in the figures) died of an apparent arsenical encephalopathy 24 h after receiving the 7th injection of 200 mg in the 2(4×200 mg) course (Duke, 1966); and after this accident no further treatment with melarsonyl was undertaken.

Having established in the earlier trials that melarsonyl had little or no direct and immediate effect on microfilariae, in some of the later trials diethylcarbamazine was used as described by Duke (1968a) in order to eliminate the residual load of microfilariae and thereby, subsequently to determine whether the adult worms were still capable of producing microfilariae.

RESULTS [1]

Observations on patients infected with the Cameroon forest strain of O. volvulus

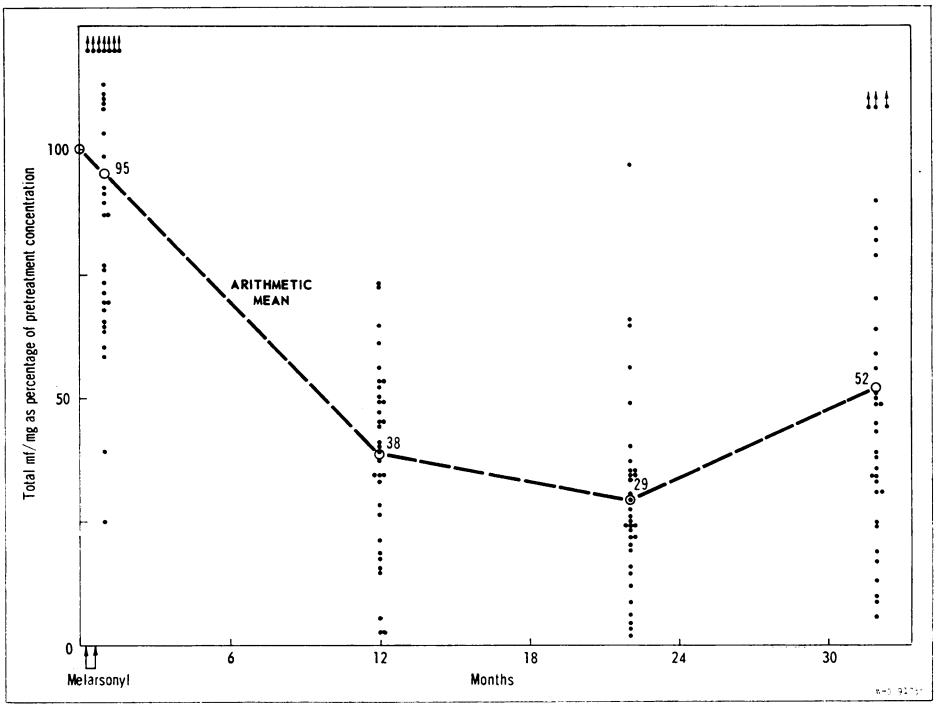
Multiple-dose course of 2(4×200 mg) melarsonyl. Fig. 1 refers to 33 patients from Weme and Baduma villages who were treated with 2(4×200 mg) melarsonyl alone. Examinations were made before treatment, 1 week after the completion of treatment, and after 12 months, 22 months and 32 months. The points in Fig. 1 show for each patient the total concentrations of microfilariae per mg (mf/mg) found at each examination; the values at each post-treatment concentration are expressed as percentages of the corresponding pretreatment figure. These percentages are plotted against time and the arithmetic mean percentage for the group at each examination is indicated.

The drug showed no significant action on microfilariae, for immediately following the course of melarsonyl the mean microfilarial concentration was still at 95% of the pretreatment figure. Thereafter the concentrations began to fall, rapidly at first to reach 38% at month 12, and then more slowly to reach 29% at month 22. By month 32, however, the mean concentration had risen again to 52%. A curve plotted from the above figures suggests that the adult

[1] The concentrations of microfilariae in individual patients are not given in this paper but are available in an unpublished document, WHO/ONCHO/68.72. A limited number of copies of this document is available to persons officially or professionally interested on request to Distribution and Sales, World Health Organization, 1211 Geneva, Switzerland.

FIG. 1

VARIATIONS IN CONCENTRATIONS OF MICROFILARIAE IN 33 ONCHOCERCIASIS PATIENTS (FOREST VILLAGES OF WEME AND BADUMA) TREATED WITH 2(4×200 mg) OF MELARSONYL POTASSIUM



worms had been killed or sterilized by the treatment, leaving the whole existing population of microfilariae undamaged and subject to a slow decline in numbers from natural mortality. However, in this environment, where heavy transmission was taking place, microfilariae from reinfections would be expected to make their appearance from about month 18 onwards. There was thus an overlap of 2 microfilarial populations, an old one declining and a young one increasing, giving the net result shown in Fig. 1.

Some confirmation of this interpretation is seen in Fig. 2, which refers to 30 patients from Mundame village who were treated with 2(4×200 mg) of melarsonyl followed by microfilaricidal diethylcarbamazine (15×200 mg Banocide at month 2, and 4×200 mg at month 3).

Again there was no immediate microfilaricidal action attributable to the melarsonyl but, after diethylcarbamazine had reduced the mean microfilarial concentration in the group to 0.7% at month 3, the mean concentration remained very low for a considerable period, reaching only 1.2% at month 13 and 6.3% at month 22. This pattern of near-zero concentrations maintained for more than 10 months indicates that virtually the whole of the original load of adult female worms had been killed or sterilized, and it was not until month 22, or more noticeably at month 38, by which time the mean concentration had risen to 36%, that new microfilariae began to appear, stemming almost certainly from reinfections.

Single doses of melarsonyl at 7.1 to 10 mg/kg with a maximum dose of 500 mg. Fig. 3 refers to 26 patients from the village of Bombele who were treated with a single dose of 500 mg or at the rate of 10 mg/kg. No diethylcarbamazine was given. The fall in microfilarial concentrations to means of 57% at month 12 and 23% at month 26 again suggests that the drug had a lethal action on at least some, and probably most of the adult worms, but it is impossible to say what proportion of the microfilariae present at month 26 stemmed from reinfections.

FIG.
VARIATIONS IN CONCENTRATIONS OF MICROFILARIAE IN 30 ONCHOCERCIASIS PATIENTS (FOREST VILLAGE OF MUNDAME) TREATED WITH 2(4×200 mg) OF MELARSONYL POTASSIUM FOLLOWED BY MICROFILARICIDAL DIETHYLCARBAMAZINE

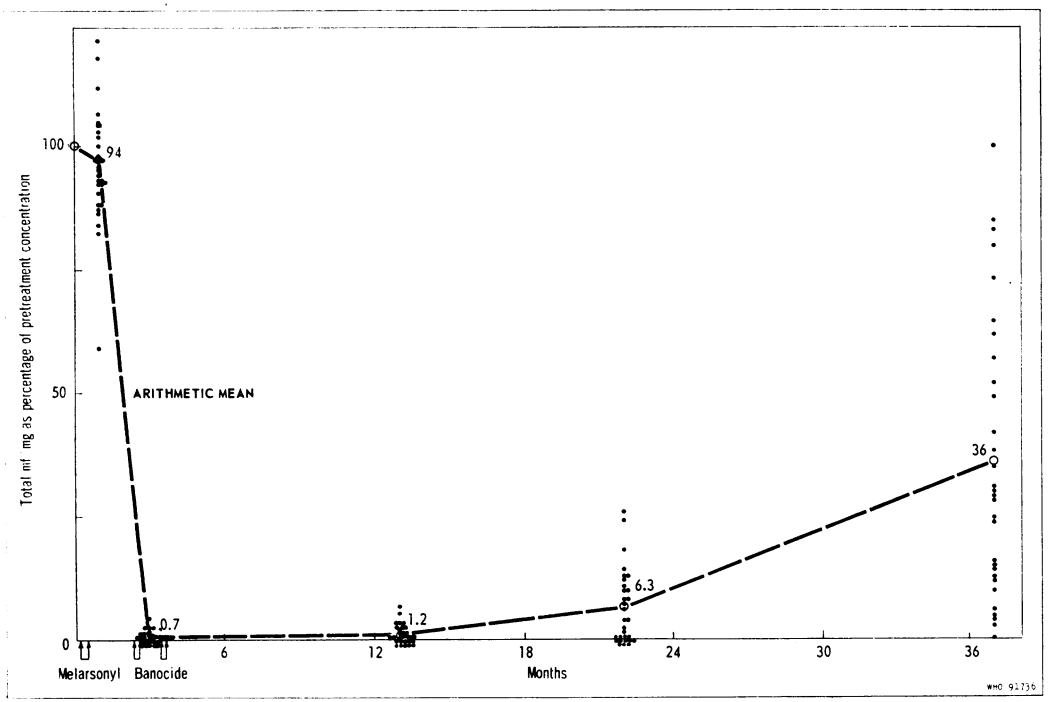


FIG. 3
VARIATIONS IN CONCENTRATIONS OF MICROFILARIAE IN 26 ONCHOCERCIASIS PATIENTS, (FOREST VILLAGE OF BOMBELE) TREATED WITH A SINGLE DOSE OF MELARSONYL POTASSIUM AT THE RATE OF 7.1 mg/kg–10.0 mg/kg

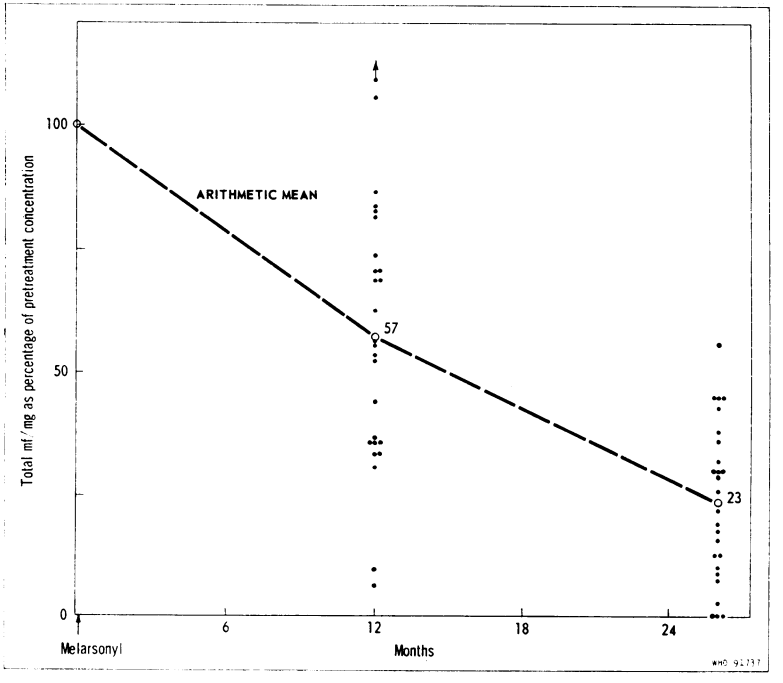


FIG. 4

VARIATIONS IN CONCENTRATIONS OF MICROFILARIAE IN 22 ONCHOCERCIASIS PATIENTS (FOREST VILLAGE OF BOLO) TREATED WITH A SINGLE DOSE OF MELARSONYL POTASSIUM AT THE RATE OF 7.1 mg/kg–10.0 mg/kg FOLLOWED BY MICROFILARICIDAL DIETHYLCARBAMAZINE

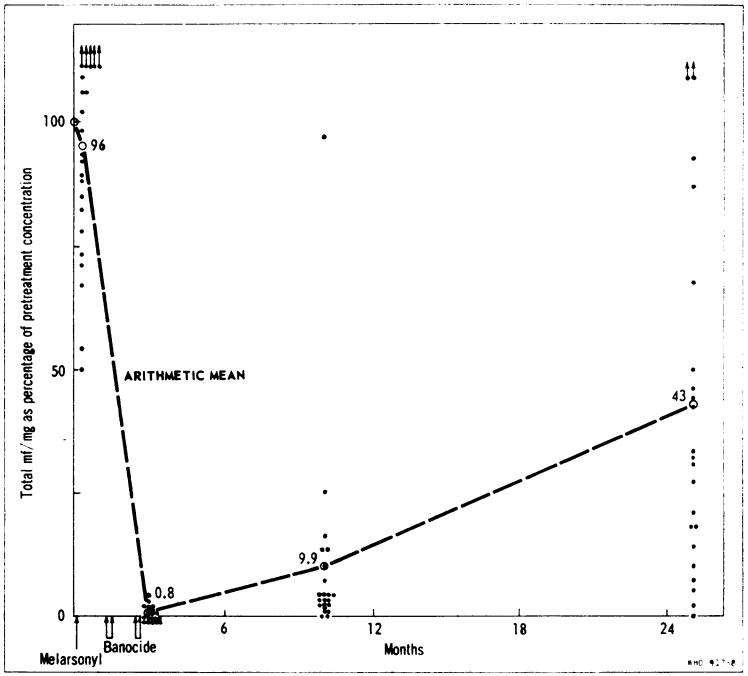


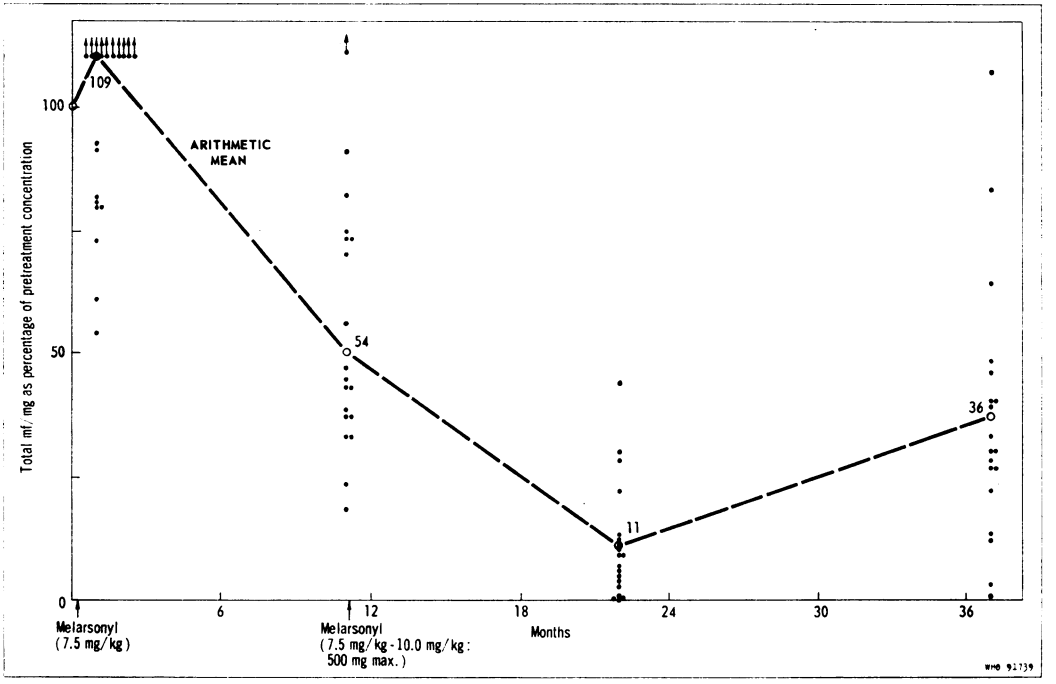
Fig. 4 refers to 22 patients from Bolo village who also received the single-dose treatment at a maximum of 500 mg or at 10 mg/kg. In this series, an immediate post-treatment examination revealed a mean microfilarial concentration of 96% and demonstrated that the single-dose treatment also had no appreciable direct effect on microfilarial concentrations. Microfilaricidal diethylcarbamazine was then given (12×200 mg Banocide at month 1, followed by 8×200 mg at month 3), and at the end of this treatment the mean concentration of microfilariae was reduced to 0.8%.

Subsequent observations were made at month 10 when the mean microfilarial concentration had risen to 9.9% over 7 months, suggesting that some but by no means all of the adult worms remained alive and fertile. In 1 patient, who had received 7.6 mg/kg of melarsonyl, the microfilarial concentration at this time had risen as high as 97%, rendering it unlikely that his adult worms had been affected at all by the drug. At month 25, by which time the mean concentrations had risen to 43%, some of the microfilariae found were undoubtedly stemming from reinfections. Nevertheless this represents a more rapid rise than the one observed in patients from the same village complex who had received the 2(4× 200 mg) course of melarsonyl (Fig. 1), which again suggests that the single-dose treatment was not entirely effective in killing the whole of the original worm load.

Single doses of melarsonyl at 7.5 mg/kg–10 mg/kg repeated at yearly intervals. Fig. 5 refers to 19 patients from Bombe, a village of moderately heavy transmission, who were given a first dose of melarsonyl at 7.5 mg/kg followed at month 11 by a further maximum dose of 500 mg or a concentration of 10 mg/kg. The mean microfilarial concentration of the group was reduced to 54% at month 11 and to 11% at month 22. It had been intended to continue these treatments on an annual basis in the hope of arriving at near-zero counts by the end of the third or fourth year, but this plan had to be abandoned as soon as the danger of arsenical encephalopathy became apparent. By the time the final examination

FIG. 5

VARIATIONS IN CONCENTRATIONS OF MICROFILARIAE IN 19 ONCHOCERCIASIS PATIENTS (FOREST VILLAGE OF BOMBE) TREATED WITH 2 SINGLE DOSES OF MELARSONYL POTASSIUM AT THE RATE OF 7.5 mg/kg–10.0 mg/kg, SEPARATED BY AN INTERVAL OF 11 MONTHS



was made at month 37, reinfections had begun to produce new microfilariae and the mean percentage concentration had risen again to 36%.

Fig. 6 refers to 16 other patients from Bombe who received a similar dosage of melarsonyl to the preceding group but who were also given diethylcarbamazine. At month 3 after the first 7.5 mg/kg dose of melarsonyl they received 15×200 mg Banocide which reduced their mean microfilarial concentration to 1.9%, only to rise again to 33% by month 11. This suggested that the initial dose of melarsonyl at 7.5 mg/kg had only a partial effect on the over-all fertility of the adult worm load. The second dose of melarsonyl was then given at month 11 (7.2 mg/kg–10.0 mg/kg with a 500-mg maximum) and followed, at month 13, by a further course of microfilaricidal diethylcarbamazine, i.e., 13×200 mg Banocide. No examination was made immediately after this second course of Banocide but it is justifiable to assume that the microfilarial concentrations were again reduced almost to zero at its conclusion. At month 22, that is 9 months later, the mean concentration of microfilariae had risen only to 5.9%, indicating that the second (and usually higher) dose of melarsonyl had achieved a further and more marked effect on the fertility of the adult female worms. At month 37, that is 26 months after the last dose of melarsonyl and with reinfections supervening, the mean concentration had risen to 30%.

Observations on patients infected with the Cameroon Sudan-savanna strain of O. volvulus.

Multiple-dose course of 2(4×200 mg) melarsonyl. Fig. 7 refers to 21 patients from Voko village and its environs who received 2(4×200 mg) melarsonyl alone. Fig. 8 refers to a further 19 patients from the same village who received the same dosage of melarsonyl followed by microfilaricidal diethylcarbamazine. Immediately after treatment there was a

FIG. 6

VARIATIONS IN CONCENTRATIONS OF MICROFILARIAE IN 16 ONCHOCERCIASIS PATIENTS (FOREST VILLAGE OF BOMBE) TREATED WITH 2 SINGLE DOSES OF MELARSONYL POTASSIUM AT THE RATE OF 7.5 mg/kg–10.0 mg/kg, SEPARATED BY AN INTERVAL OF 11 MONTHS AND FOLLOWED IN EACH CASE BY MICROFILARICIDAL DIETHYLCARBAMAZINE

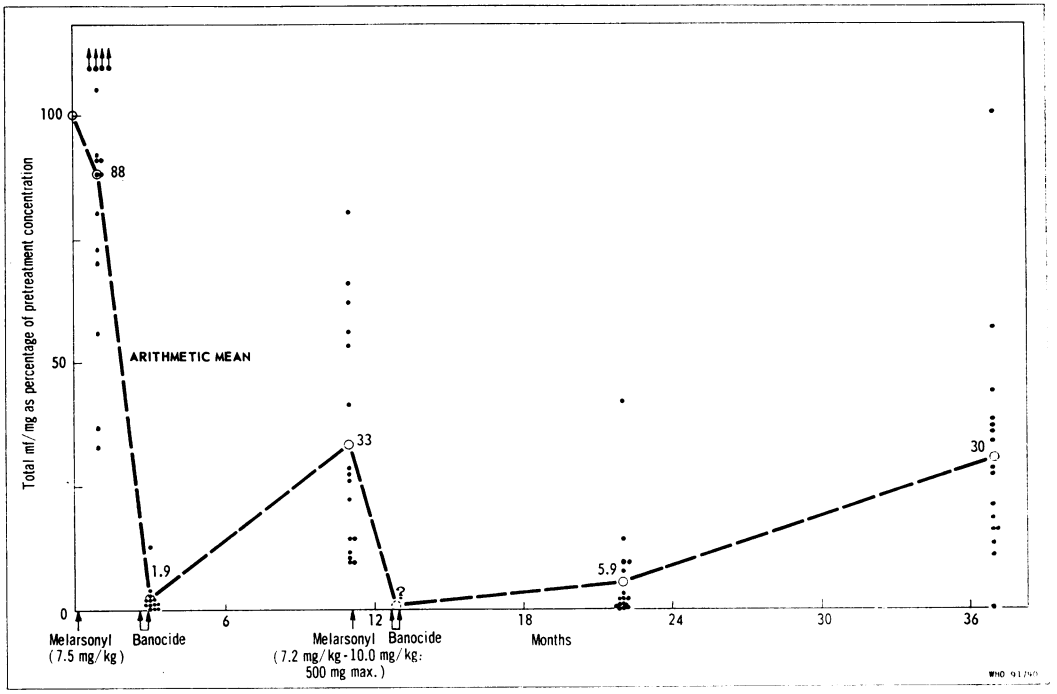


FIG. 7

VARIATIONS IN CONCENTRATIONS OF MICROFILARIAE IN 21 ONCHOCERCIASIS PATIENTS (SUDAN SAVANNA VILLAGE OF VOKO) TREATED WITH 2(4×200 mg) OF MELARSONYL POTASSIUM

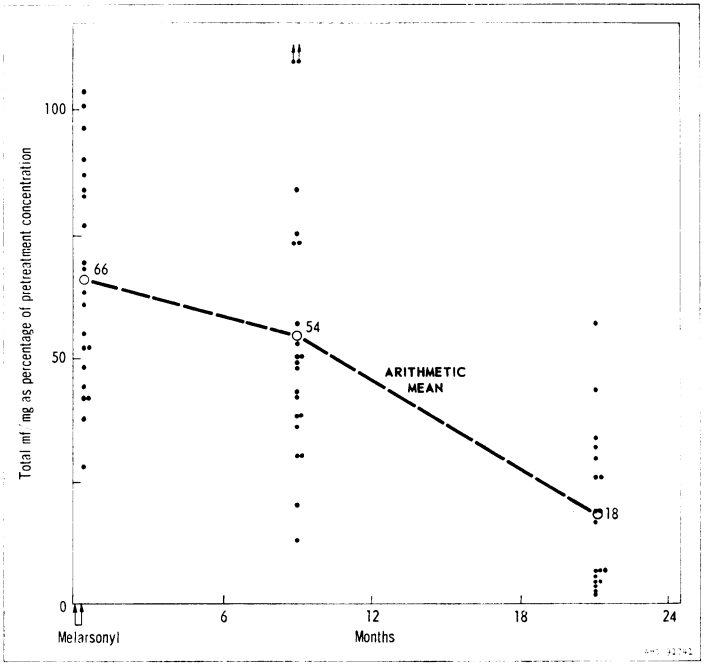
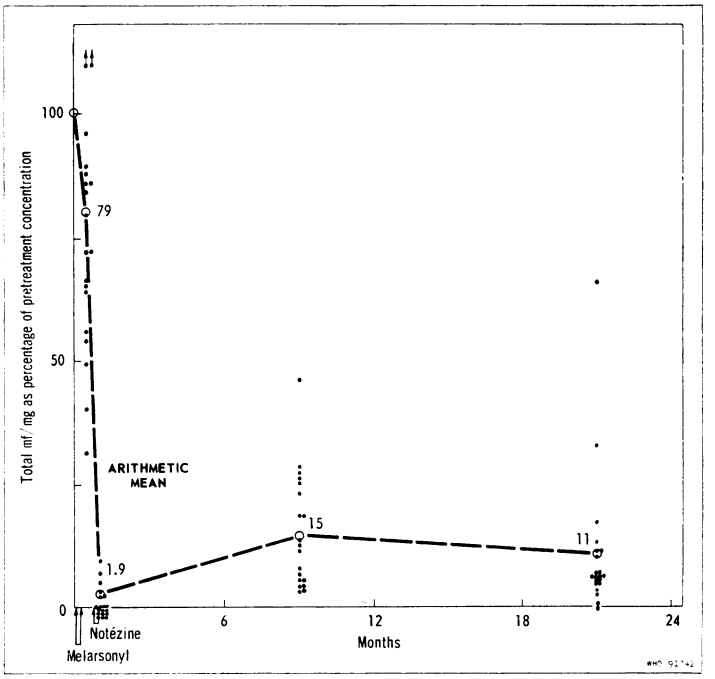


FIG. 8

VARIATIONS IN CONCENTRATIONS OF MICROFILARIAE IN 19 ONCHOCERCIASIS PATIENTS (SUDAN SAVANNA VILLAGE OF VOKO) TREATED WITH 2(4×200 mg) OF MELARSONYL POTASSIUM FOLLOWED BY MICROFILARICIDAL DIETHYLCARBAMAZINE

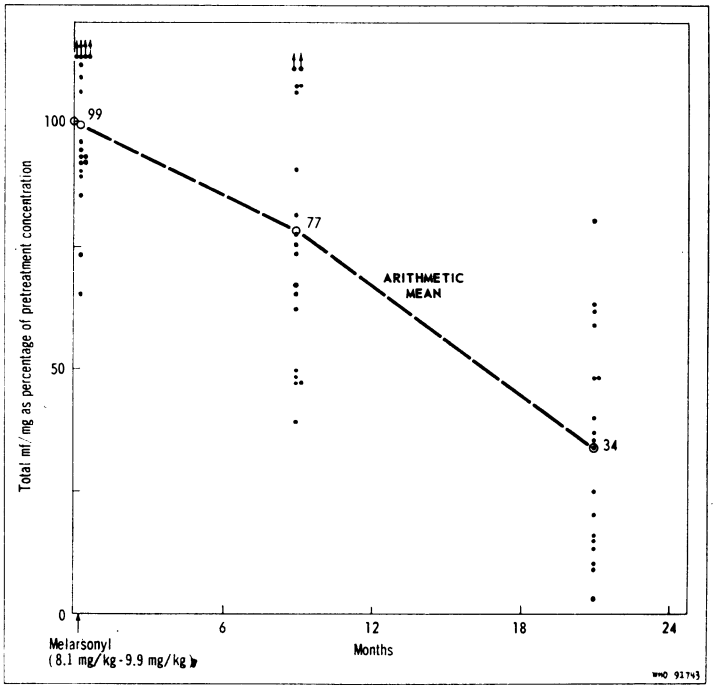


significant reduction in the mean concentration of microfilariae to 66% in the first group and to 79% in the second group, giving a combined mean of 72%. This indicates that against the Sudan savanna strain in this particular environment the drug had a slight microfilaricidal action in its own right. However, there was no detectable correlation in individual patients between the degree of microfilaricidal action and the total dosage of melarsonyl in mg/kg.

In the first group (Fig. 7), which received no diethylcarbamazine, the mean concentration of microfilariae continued to fall slowly after treatment to reach 54% at month 9 and 18% at month 21. There is no information available on the rate at which reinfections developed in the Voko environment but it would appear from these figures that the 2(4×200 mg) course of melarsonyl had a considerable effect on the adult worms. This belief receives support from the 19 other Voko patients (Fig. 8) who received microfilaricidal diethylcarbamazine (16×100 mg Notézine over 1 week) starting about 14 days after the end of their 2(4×200 mg) course of melarsonyl. For practical reasons, on account of the remoteness of the area and the difficulty of assembling the patients, the diethylcarbamazine had to be given to this group sooner after completing the melarsonyl course than has been the case in comparable trials in the forest zone. It was probably given before all the microfilariae from the dead or moribund worms had reached the skin and perhaps before the full effect of the melarsonyl on the adult worms had been produced. Immediately after the administration of the diethylcarbamazine, the mean microfilarial concentration was reduced to 1.9%. At month 9 it had risen again to 15%, but at month 21, apart from a single patient, no further significant rise was observed and in 13 patients there had been a fall. The mean concentration was thus reduced to 11%. The most probable interpretation of these findings is that the adult worms had been killed or sterilized by the melarsonyl but that a

FIG. 9

VARIATIONS IN CONCENTRATIONS OF MICROFILARIAE IN 18 ONCHOCERCIASIS PATIENTS (SUDAN SAVANNA VILLAGE OF DJELOPO) TREATED WITH A SINGLE DOSE OF MELARSONYL POTASSIUM AT THE RATE OF 8.1 mg/kg–9.9 mg/kg



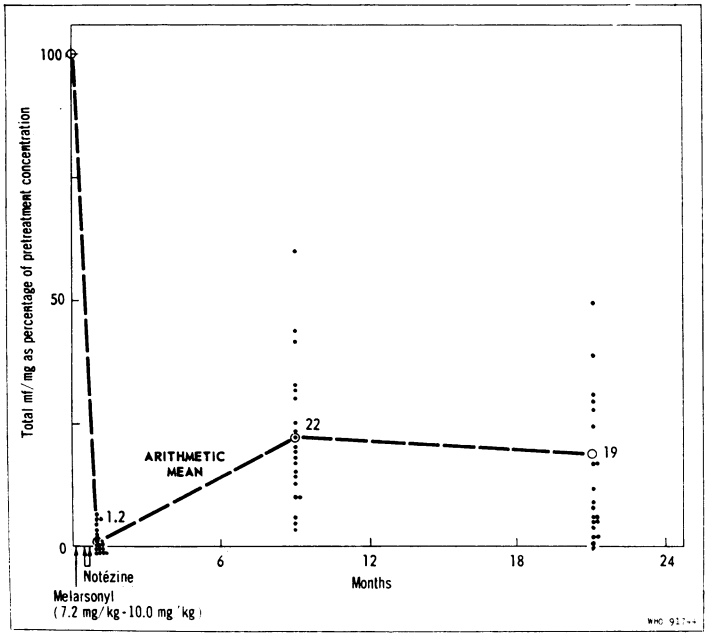
small population of residual microfilariae had arrived in the skin after the diethylcarbamazine had been given. These, being very young microfilariae, had died off very slowly thereafter.

Single doses of melarsonyl at 7.2 mg/kg – 10 mg/kg with a maximum dose of 500 mg. Fig. 9 refers to 18 patients from Djelopo village and its environs who received a single maximum dose of 500 mg of melarsonyl or a concentration of 10 mg/kg.

No immediate action on microfilariae was observed following this dosage, the mean microfilarial concentration 1 week after treatment being 99%. Thereafter a fall in microfilarial concentrations was observed at much the same rate as that following the 2(4×200 mg) melarsonyl course, giving mean concentrations at month 9 and month 21 of 77% and 34%, respectively. Again a lethal and sterilizing action on the adult worms appears to have resulted from treatment, and again this is borne out to some extent by the further group of 21 patients from the same village who are recorded in Fig. 10. This latter group received microfilaricidal diethylcarbamazine (20×100 mg Notézine over 1 week) about 2 weeks after their dose of melarsonyl and for the reasons stated above the microfilaricidal treatment had also to be given earlier than was desirable. Immediately after the diethylcarbamazine the mean microfilarial concentration was reduced to 1.2 per cent. The pattern of microfilarial concentrations at the succeeding examinations was similar to that seen after the multidose course. At month 9 the mean had risen to 22%, but at month 21 the counts had fallen again in 13 patients and had continued to rise only slowly in 8 others, giving a mean concentration of 18% for the groups as a whole. It would appear that the single-dose treatment had a considerable effect on the adult worms but one which was less marked than that produced by the multiple-dose course.

FIG. 10

VARIATIONS IN CONCENTRATIONS OF MICROFILARIAE IN 21 ONCHOCERCIASIS PATIENTS (SUDAN SAVANNA VILLAGE OF DJELOPO) TREATED WITH A SINGLE DOSE OF MELARSONYL POTASSIUM AT THE RATE OF 8.1 mg/kg–9.9 mg/kg, FOLLOWED BY MICROFILARICIDAL DIETHYLCARBAMAZINE



DISCUSSION

Effect on microfilariae

Melarsonyl clearly has very little microfilaricidal action. In none of the series of patients receiving doses at the rate of 7.1 mg/kg–10 mg/kg was any significant immediate reduction in mean microfilarial concentrations observed. Against the forest strain of *O. volvulus* the multiple-dose course showed no significant microfilaricidal action, but against the Sudan-savanna strain some action was detected. In 36 out of 40 patients receiving the 2(4×200 mg) melarsonyl course at Voko (Fig. 7 and 8) the microfilarial concentration was reduced immediately following treatment, the mean figure for the whole group being 72%. The fall in microfilarial concentration in individual patients showed no relation to the total dose of melarsonyl in mg/kg. It may be that the microfilariae of the Sudan-savanna strain are more susceptible to the drug than are those of the forest strain, but it is impossible to exclude other factors, such as the rate of metabolism of the drug by the host, which may also have differed in the 2 environments and which might have affected the issue.

Effect on adult warms

Multiple-dose course. The effect of the multiple-dose course on the adult worms was obviously very considerable and probably amounted in most cases to an elimination of the adult female worm load. Since melarsonyl has very little action on microfilariae, and as the microfilariae have a life-span which can be as long as 24–30 months, it is difficult to demonstrate the macrofilaricidal action of melarsonyl in patients living in areas of heavy transmission where they are continually exposed to reinfection. Nevertheless there is a clear pattern of steadily declining microfilarial concentrations over periods of 15–26 months following the multiple-dose melarsonyl treatment, and an absence of any build-up of microfilarial concentrations before the time when post-treatment reinfections would be expected to mature. Furthermore in those experiments in which the residual microfilarial population was eliminated by diethylcarbamazine given 1–3

months after melarsonyl, there was no significant build-up of microfilariae over the ensuing 10–19 months, and the counts remained close to zero until reinfections supervened. This pattern is quite distinct from that seen when microfilariae are eliminated by diethylcarbamazine in patients who have received no macrofilaricidal treatment; in these circumstances, as described by Duke (1957, 1968a), microfilariae reappear immediately and the pretreatment concentration is usually attained within 6–36 months.

In the present experiments, and using the method here described, no excised nodules were examined. However, in 2 patients treated with the 2(4 × 200 mg) melarsonyl course, who were not exposed to reinfection and whose microfilarial concentrations declined to zero over the ensuing 30 months, excision of all palpable nodules at the end of this period revealed all the worms to be dead, fibrosed and calcified (Friedheim, 1964; Duke, 1968a).

Single-dose treatment. The effect of the single-dose treatment was not so marked, but in some individuals it is almost certain that the drug had killed all the adult worms. In the groups treated with a single 500-mg dose, giving a concentration of melarsonyl between 7.5 mg/kg and 10 mg/kg, the effect was more pronounced than in those receiving 7.5 mg/kg only.

Single doses were sufficiently promising to make it worth while repeating the treatment at yearly intervals in an attempt to kill the original load of adult worms, together with those maturing from reinfections, and thus maintain the individual free from fertile adult worms for a period exceeding the lifespan of the longest-lived microfilariae. An experiment on these lines was started at the forest village of Bombe. Those patients (Fig. 6) who received diethylcarbamazine after their first dose of melarsonyl at 7.5 mg/kg demonstrated that not all the adult worms were killed by the first dose of melarsonyl, for the mean microfilarial concentration rose from 2.3% just after the diethylcarbamazine to reach 33% 8 months later. A second and higher dose of melarsonyl (500 mg) was then given and again followed by diethylcarbamazine. Over the ensuing 9 months the mean microfilarial concentration rose from near zero to no more then 5.9%. In the other group of patients from Bombe village (Fig. 5), who received no diethylcarbamazine but were otherwise treated similarly with 2 annual doses of melarsonyl, the mean microfilarial concentration had fallen to 11% by the 22nd month after the first dose. Unfortunately, at this point it became necessary to stop the trial as the risks of arsenical encephalopathy associated with melarsonyl had become apparent. However, it would appear that if the treatment had been continued by giving third and fourth doses of 500 mg melarsonyl at the 23rd and 35th months respectively, then in all probability the microfilarial counts would have been reduced to zero by about the 30th month and the patients' loads of adult worms would have been eliminated despite continued reinfection. Such an occurrence has indeed been demonstrated elsewhere in a single patient who received 3 annual doses of melarsonyl (Duke, 1968d).

This method, in which a pure macrofilaricide is used at approximately yearly intervals, has obvious possibilities in control of onchocerciasis. Theoretically it would be possible to eliminate the human microfilarial reservoir by this means alone within a period of 3 years, and thus to break the transmission cycle. Unfortunately, on account of the drug's toxicity, the method cannot at present be further tested in the field using melarsonyl as the macrofilaricide; but if the danger of encephalopathy could be overcome without loss of therapeutic effect, melarsonyl might well prove to be a most useful weapon in onchocerciasis control.

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RÉSUMÉ

EFFETS DE LA CHIMIOTHÉRAPIE SUR *ONCHOCERCA VOLVULUS* : 4. ESSAIS DE TRAITEMENT PAR LE MÉLARSONYL POTASSIQUE

On a étudié les effets d'un composé organo-arsenical, le mélarsonyl potassique, sur *Onchocerca volvulus* chez des malades infectés par des souches de parasites originaires de la forêt camerounaise et de la savane soudanaise. Deux schémas de traitement par voie intramusculaire ont été essayés. Le premier consistait en quatre doses quotidiennes et consécutives de 200 mg, le traitement étant répété après un intervalle de 10 à 14 jours; la dose totale était donc de 2 (4 × 200 mg). Le deuxième schéma comprenait une dose unique de 7,1 à 10 mg/kg, avec un plafond de 500 mg.

Dans la plupart des essais, le médicament n'a pas exercé d'action immédiate sur les concentrations microfilariennes. On a observé une légère action microfilaricide à l'égard de la souche originaire de la savane soudanaise en utilisant le schéma 2 (4 × 200 mg). L'administration de 2 (4 × 200 mg) de mélarsonyl s'est montrée capable de tuer ou de stériliser la plupart ou la totalité des vers femelles adultes chez les malades ainsi traités, tandis que les populations résiduelles de microfilaires ont diminué graduellement par mortalité naturelle au cours des deux années qui ont suivi le traitement. Ces microfilaires résiduelles ont pu être tuées par l'administration de diéthylcarbamazine. Les doses uniques de mélarsonyl, administrées à raison de 7,1 à 10 mg/kg, n'ont pas provoqué une létalité ou une stérilisation aussi marquées des vers adultes, mais on pense que si l'administration d'une dose de l'ordre de 10 mg/kg pouvait être répétée chaque année, elle permettrait d'éliminer chez les malades toutes les microfilaires dans un délai de trois ans.

Les risques d'encéphalopathie arsenicale interdisent actuellement l'emploi du mélarsonyl potassique dans le traitement de l'onchocercose; toutefois, si l'on parvenait à neutraliser ce danger, le médicament pourrait rendre de très grands services pour des campagnes de lutte fondées sur une chimiothérapie massive.

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