FOLIA PARASITOLOGICA (PRAHA) 28: 235–242, 1981.

THE USE OF MEBENDAZOLE IN THE TREATMENT OF TRICHINELLOSIS IN MAN

T. MITTERMAYER and R. ŠPALDONOVÁ

Clinic of Infectious Diseases, University Hospital, Košice, and Helminthological Institute, Slovak Academy of Sciences, Košice

Abstract. A description is given of an epidemic of trichinellosis in the districts of Košice and Rožňava, Slovakia. The confirmed cause of the epidemic was the consumption of wild hog meat which had escaped a veterinary meat inspection. The course of infection was apparent in 10 patients, inapparent in 16. Mebendazole in doses from 100—600 mg/day was administered for 6—10 days to 9 patients with a clinically apparent, and to one patient with an inapparent infection. Both the clinical course and results of a biopsy examination suggested that the doses had not been high enough for a positive effect of the treatment. Two years after the acute stage of trichinellosis, we repeated the treatment in one patient using a dose of 1000 mg/day of mebendazole for a period of 14 days. An improvement of the clinical picture and results of a biopsy examination supported our assumption that an effective treatment of acute trichinellosis requires high doses of mebendazole.

Until recently, trichinellosis had been regarded as an uncurable infection. The first evidence on the effect of thiabendazole on all *Trichinella* stages in mice and pigs including the muscle stage was obtained by Campbell (1961) and Campbell and Cuckler (1962). The first cases of a causal treatment of trichinellosis in man with this drug were described by Stone et al. (1964) and Kean and Hoskins (1964). Later syntheses of a number of benzimidazole compounds disclosed the widest spectrum of efficacy for methyl 5,6 benzoyl 2-benzimidazolecarbamate called mebendazole (Vermex R). The drug was tested on *Trichinella*-infected rats by Thienpont et al. (1974), on artificially infected white mice by Špaldonová et al. (1974). Both studies confirmed that the effect of the drug was highly potent on all phases of experimental trichinellosis.

The incidence of trichinellosis was shown to be endemic and sporadic in eastern Slovakia (Mittermayer 1973). Its 10th epidemic outbreak occurred in December 1976 and January 1977. The present paper describes the results obtained in the treatment of trichinellosis in man with mebendazole.

MATERIALS AND METHODS

In November 1976, a wild hog was killed by hunters in the Rožňava district. Without having the meat inspected with trichinoscopy, it was minced, made into sausages, smoked and consumed by the hunters' families and their friends. Of those who had eaten the sausages, the infection was apparent in 10 patients, inapparant in 16 patients. The diagnosis was confirmed both by a positive finding of Trichinellae in the sausages and by a biopsy examination of muscles of the patients. These findings provided conclusive evidence for the incidence of trichinellosis in the patients. In several of these, the course of infection was particularly severe. In one case, the clinical picture was dominated by breathing difficulties, in two other cases, the dominant feature was a symptomatology of the central nervous system, i.e., with signs of a rightsided hemiparesis in one patient, in the other with the picture of an encephalitis with unconsciousness lasting for one month, combined with epileptiform paroxysms (Mittermayer et al. 1979).

Basing on promising results obtained in the treatment of experimental trichinellosis (Thienpont et al. 1974, Špaldonová 1973, Špaldonová et al. 1974), we decided to use mebendazole (Vermox) for 10 patients, one with an inapparent and 9 with an apparent infection. Of these,

Table 1. Survey of mebendazole doses and results of muscle biopsies made after the treatment of trichinellosis

Name and age	Day of infestation	Day of disease	Clinical form	Weight of patient in kg	Daily dose of mebendazole and duration of application	Dose of mebendazole/kg weight	Total dose	Muscle biopsy after treatment at day	Compressoric finding of larvae
Ing. D. P. 35	22	7	apparent	85	200 mg/day—10 days	2.2 mg/kg	2000 mg	8	3 larvae
D. M. 24	34	3	apparent	62	200 mg/day—7 days 400 mg/day—3 days	3.2 mg/kg	2600 mg	5	2 live 3 dead
V. P. 17	34	5	apparent	51	200 mg/day—7 days	3.9 mg/kg	1400 mg	5	negative
V. P. 20	37	9	apparent	78	200 mg/day—7 days	2.5 mg/kg	1400 mg	—	—
V. L. 16	37	8	apparent	70	200 mg/day—7 days	3.0 mg/kg	1400 mg	—	—
Dr. V. A. 33	59	29	apparent	70	300 mg/day—6 days	4.5 mg/kg	1800 mg	1	2 live 3 dead
Dr. K. J. 35	65	—	inapparent	95	600 mg/day—3 days 300 mg/day—4 days	6.3 mg/kg 3.1 mg/kg	3000 mg	1	negative
D. V. 42	74	52	apparent	80	200 mg/day—9 days	2.5 mg/kg	1800 mg	63	4 live
D. S. 23	70	51	apparent	76	300 mg/day—1 day 200 mg/day—8 days	3.9 mg/kg	2100 mg	3	22, some dead
H. A. 22	not identified	30	apparent	58	200 mg/day—10 days	3.4 mg/kg	2000 mg	4	negative

7 patients were treated from 7—10 days with daily doses of 200 mg, two patients for 6 days with 300 mg/day. The doses administered to the one patient with an inapparent course of infection were 600 mg/day for 3 days, and 300 mg/day for the following 4 days. One patient (D.M.) complaining of persisting difficulties after this treatment was given an additional dose of 400 mg of mebendazole for the following 3 consecutive days (Table 1). Apart from two patients complaining of anorexia and nausea, the drug was found to be compatible. To 7 patients, mebendazole was administered during the acute, febrile phase of the disease, to another two patients after the acute, clinical phase, to one patient during an inapparent course of the infection.

RESULTS

The clinical, therapeutic effect of mebendazole administered during the acute phase of infection in the mentioned doses was not found to be greatly better than that obtained in the treatment of trichinelloses with thiabendazole (3 g/day) used in the treatment of trichinellosis in 1975 (Mittermayer et al. 1978). E.g., in the patient D.P. for whom a 10 day-treatment with mebendazole (200 mg/day) had been prescribed, a high temperature and acute signs of trichinellosis were still present at day 6 of the treatment. Owing to the severe clinical picture, the patient was given orally a daily dose of prednison (20 mg) for 9 days. It was effective in that both the fever and acute clinical symptoms subsided within the next 24 hr. In most patients with an apparent infection, both a subfebrile temperature and subjective difficulties persisted after the treatment for a prolonged period. Two patients recovering from a most severe, clinical form of trichinellosis, suffered from subfebrile temperatures combined with myalgia mainly after a physical stress in spite of the mebendazole treatment. Of two other patients for whom treatment had started at as late a time as days 51 and 52 p.i., one suffered from subfebrile temperatures with a mild myalgia after a heavier physical load for another two years. After the treatment, a biopsy was made of the m. deltoideus of 8 patients (Table 1). In addition to dead, decomposed larvae, we found two viable larvae in the compressed biopsy (Figs. 1, 2).

An evaluation was made of eosinophile leukocytes for all patients treated. Prior to the treatment, their level ranged from 15—40 %, immediately after the treatment, they increased in number in most patients, but several days later, they decreased gradually to physiological values.

All patients treated with mebendazole, and mainly those with objective difficulties, were under observation for a prolonged period. The patient D.S. who had been treated with mebendazole (2 × 100 mg/day) for 9 days in February 1977, complained of persisting difficulties such as myalgia, fatigue, a sensation of muscle fever and subfebrile states mainly after a heavier, physical stress. Two years later, i.e., in February 1979, a biopsy was made of the musculus deltoideus. Trichinelloscopy disclosed 5 viable larvae in 0.54 g of muscle tissue. It was evident from this finding that the dose of mebendazole administered in 1977, had not been potent enough to liquidate the infection. Therefore, encouraged by favourable results in the treatment of man (Sonnet and Thienpont 1977), we decided to retreat the patient in March 1979 using higher doses of mebendazole than at the previous treatment. We started with 600—800 mg/day, and then administered 1000 mg/day for a fortnight. Apart from a slight diziness towards the end of the treatment, the drug was well suffered by the patient. For the time of the treatment, the muscles were sensitive, and there was a temporary increase in the temperature. In our opinion, both symptoms should be ascribed to an activation of the local muscle process and a resorption of decomposed substances. The patient's state was generally improved after the treatment, he felt less tired, refreshed, the pain in his muscles was subsiding. A new biopsy from the m. deltoideus was made 14 days after the treatment in order to determine the effect

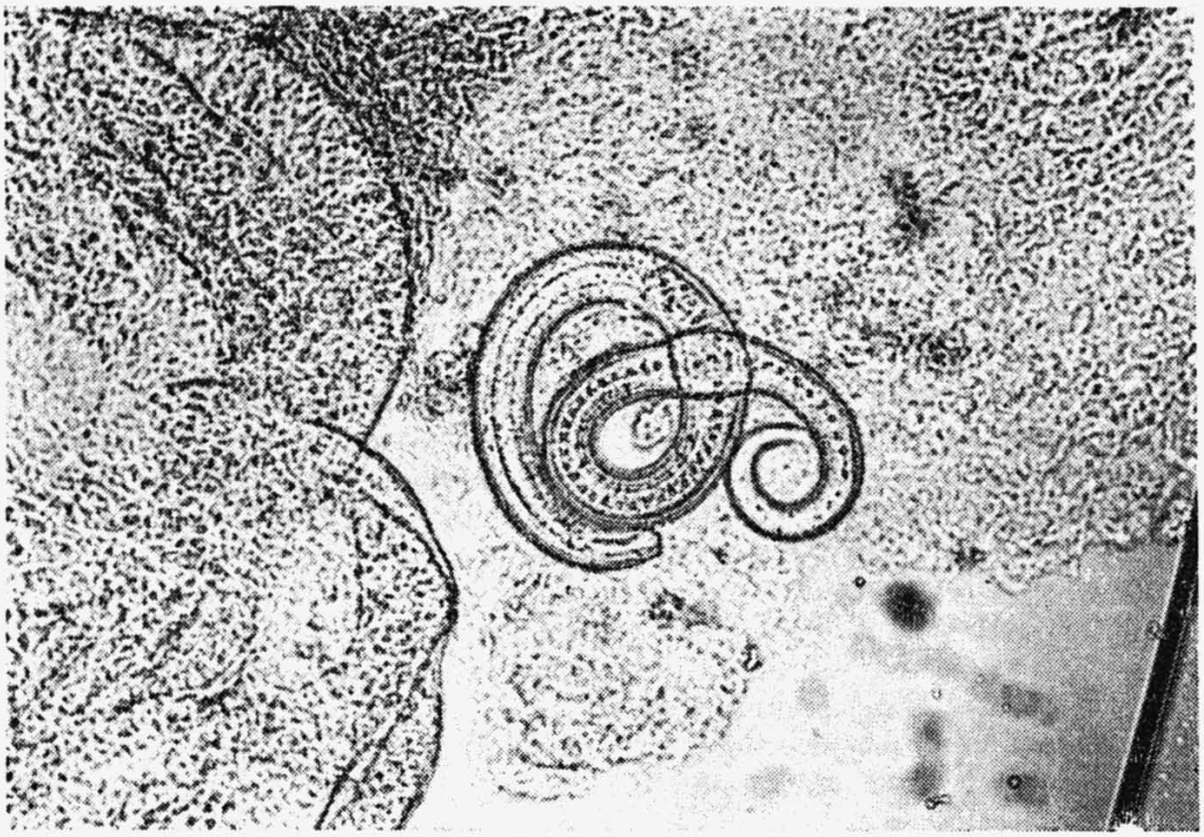

Fig. 1. Viable larva of *Trichinella spiralis* from the muscle of D.S. at day 3 after mebendazole treatment ($\times 40$).

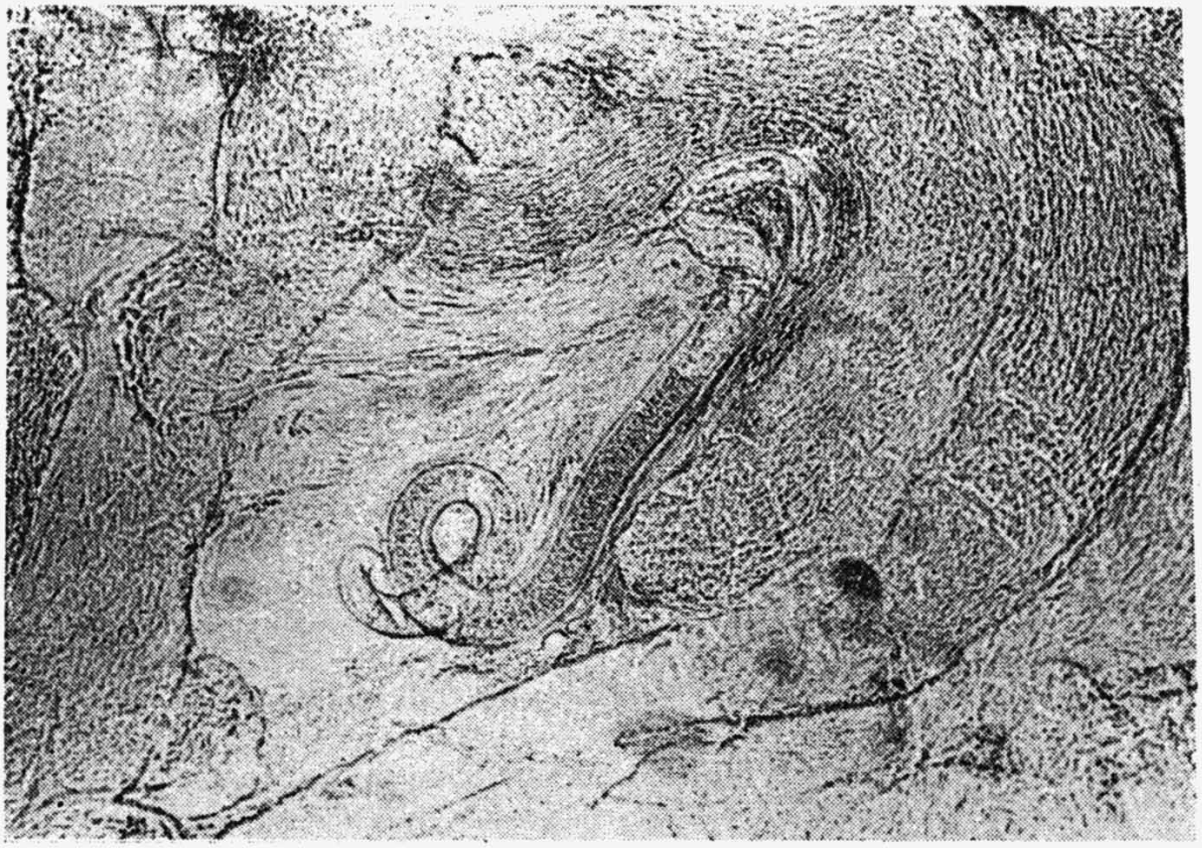

Fig. 2. Dead larva of *Trichinella spiralis* from the muscle of D.S. at day 3 after mebendazole treatment.

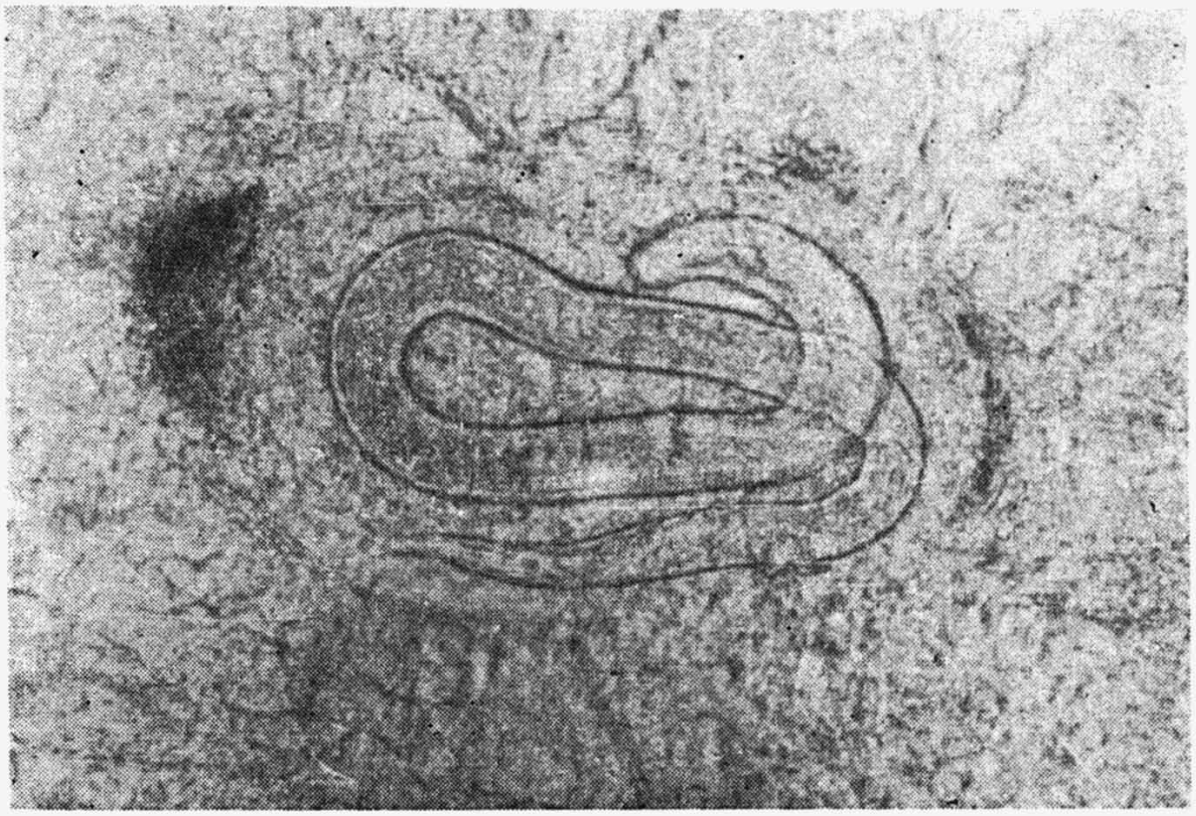

Fig. 3. Dying larva of *Trichinella spiralis* from the muscle of D.S. at day 14 after mebendazole treatment ($\times 40$).

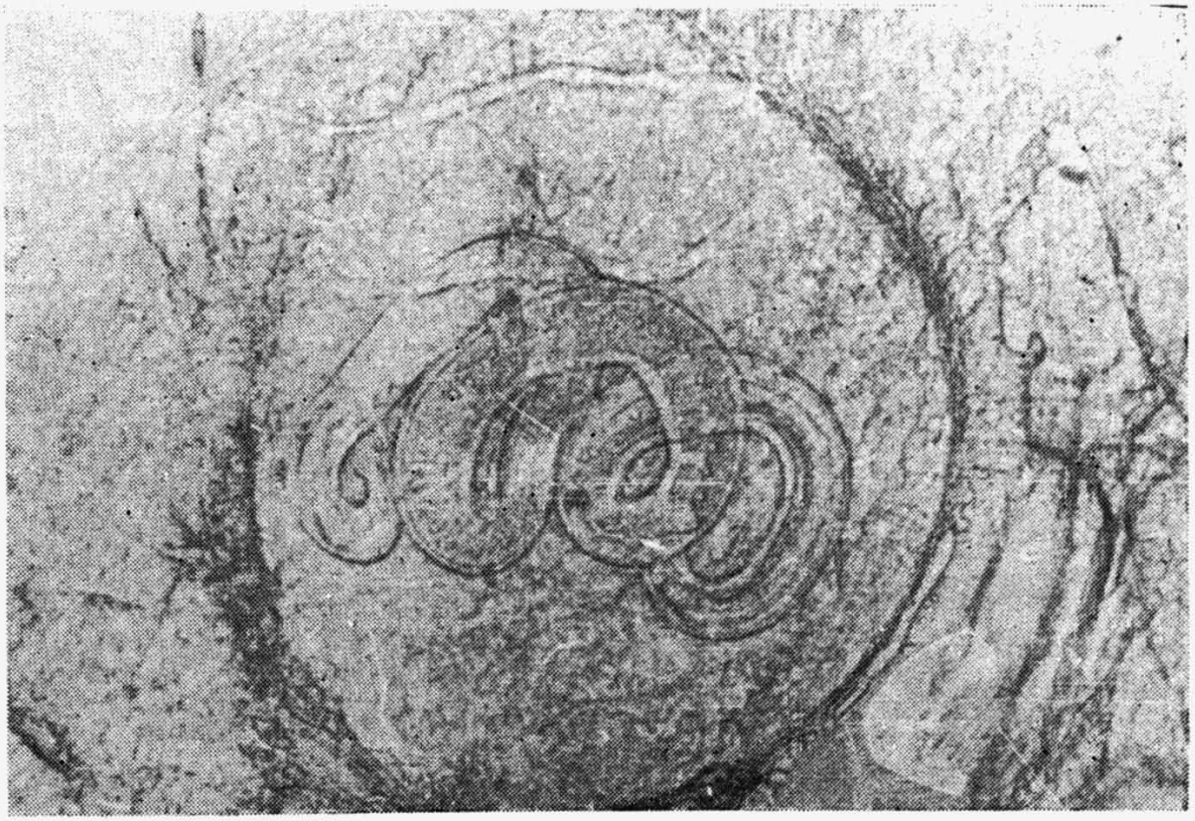

Fig. 4. Dying larva of *Trichinella spiralis* in an affected cyst from the muscle of D.S. at day 14 after treatment. Note intracapsular, cellular infiltration ($\times 40$).

of the treatment. We found 11 dying or dead larvae in 0.9 g of muscle tissue (Figs. 3, 4). A feature characteristic of all these larvae was their atypical capsule, an edematous swelling of larvae which were either dying or dead. The intracapsular, cellular, inflammatory reaction is shown in Fig. 4.

Using the indirect immunofluorescence test, we examined sera of patients partly for diagnostic purposes, partly with the intention of disclosing inapparent forms. For patients with an apparent infection, values ranged from 1 : 128 to 1 : 512. In a group of persons with an inapparent course of the infection, schoolmates of one of our infected patient who had all tasted the incriminated sausage during one of the breaks at school, we disclosed 9 cases in which the originally negative IFAT values had increased to 1 : 32 — 1 : 64 within one month.

DISCUSSION

Our results of the treatment of 10 patients infected with trichinellosis during the last epidemic in 1976—1977, with mebendazole in doses described in the text, did not confirm the highly potent effect of this drug (96—100 %) on muscle Trichinellae in experimental animals reported by Thienpont et al. (1974) and Špaldonová et al. (1974). In addition to dead larvae which had mostly been released from their capsules, we found also live larvae. The difference in the efficacy of the drug was evidently caused by higher doses of the drug (20—100 mg mg/kg) given by the authors to experimental animals. Therefore, our main problem was the dosage of mebendazole. We could neither base on doses used in the treatment of enterobiasis, i.e., a single dose of 100 mg mebendazole, nor on those used against trichocephaliasis (2 × 100 mg for 3 days) because we knew that these would be too low in the treatment of trichinellosis in man. In addition, there was a complete lack of literary data on the dosage of mebendazole to be used in the treatment of trichinellosis in man at the time of the epidemic in 1976. Therefore, knowing, that the therapeutic range of the drug was of considerable width, we prolonged its administration (from 7—10 days) and increased simultaneously the daily doses (300, 400, 600 mg). One of our patients, a physician (Dr. K. J.) fearing that the sofar inapparent course of the infection might become clinically apparent, asked to be given initial doses of 600 mg/day mebendazole which we did on his own responsibility. In all other cases, we did not dare to expose our patients to the danger evolving from the administration of too high a dose of the drug being well aware of the fact that doses given to experimental animals cannot be compared with those given to man.

An improvement in the clinical picture after the treatment with thiabendazole reported by Kean and Hoskins (1974), although biopsy showed that the drug had been unable to kill a majority of larval *Trichinella spiralis*, should evidently be ascribed to the antiinflammatory, antipyrogenic and analgesic effect of thiabendazole, which are properties suggested also by Campbell (1971) for this drug. Similar properties might be expected to be present in mebendazole.

Unfortunately, we learned much later of satisfactory results obtained by a number of authors with the use of higher doses of mebendazole. The treatment was followed by a relatively speedy retreat of both clinical symptoms and laboratory changes. However, the authors failed to determine histologically the effect of the drug during the treatment.

Sonnet et Thienpont (1977) described the treatment of two patients with mebendazole during the acute phase of trichinellosis. The treatment was started at day 24 of the infection and continued for 14 days. The daily dose of mebendazole administered to the patients was about 1 g. After 3 days of the treatment, symptoms

of the toxic, febrile stage were subsiding, and a dramatic reduction occurred both in the blood eosinophilia and in the activity of the serum of the keratinous phosphokinase. One of the patients complaining of unbearable muscle pains was given an additional dose of 25 mg prednison for 8 days. However, muscle difficulties persisted in a residual form for 6 weeks after the treatment with mebendazole; in the other patient, they persisted for 4 weeks. The drug was compatible with both patients and there were no side-effects.

Vuješević et al. (1978) used mebendazole in the treatment of 12 patients with trichinellosis. After 24—48 hr of the treatment, all patients responded to the drug with defervescence and a subsidization of symptoms typical of trichinellosis. The drug was administered orally, in the form of tablets (100 mg) for 10 days; 9 patients at the acute phase of infection received 3 × 1 tablet a day for 4 days, then 2 tablets twice a day for the next 6 days. Three patients, all at the chronical stage, were each treated individually with a different daily dose of mebendazole for 14 days, i.e., 3 times one tablet, 4 times one tablet, 5 times one tablet.

The fact that the effectivity of mebendazole depended on the height of the dose administered, was confirmed by the greatly improved clinical picture of the patient D. S., who was retreated two years after the first treatment with high doses of mebendazole (1000 mg/day for 14 days). A muscle biopsy made 14 days after the treatment disclosed a disturbance in the structure of all 11 larvae recovered.

In our opinion, satisfactory results are obtained from a compressed muscle biopsy. In doubtful cases, the sample is digested artificially. We found that days 8 to 10 after the treatment were optimal for an evaluation of the trichinellocidal effect of mebendazole in biopsy. This was confirmed by a series of experimental mice, killed in groups and examined each day, i.e., from day 1 to day 28 after the treatment with mebendazole (Špaldonová and Čorba 1977).

Our results of a muscle biopsy from the patient D. Š. were in agreement with the findings by Thienpont et al. (1974), the results obtained by de Nollin et al. (1974), and with the conclusions made by Pereverzeva et al. (1976). The first authors studied the histopathological effect on *Trichinella*-infected rats. The second authors made an electron microscopic study on the effect of mebendazole on encapsulated Trichinella larvae from mice. Pereverzeva et al. (1976) made a histomorphological study on the trichinellocidal activity of mebendazole in mice. According to the conclusions of these authors, mebendazole disturbed the formation of the capsule to the effect that it developed in an atypical shape, and caused a gradual, two-phase destruction of larvae starting with an activation of an inflammatory, cellular reaction at days 15—20 after the treatment, and followed by their destruction, resorption and hyaline degeneration of the intracapsular sarcoplasm.

A muscle biopsy from a patient made 14 days after the treatment, i.e., during the first stage of larval destruction, disclosed edematously swollen larvae with atypically shaped capsules, and the presence of a circumscribing and intracapsular, inflammatory phagocytosis. Basing on the promising therapeutic results after the re-treatment of the patient D. S., it was decided to re-treat all those patients from the last epidemic in whom difficulties were persisting.

According to a personal communication, Thienpont suggested for the treatment of the acute stage of trichinellosis the use of these doses of mebendazole: For the first 3 days 1 g/day, for the next 3 days 2 g/day, for the following 6—10 days 30—50 mg/kg weight/day. For serious states he recommended also glycocorticoides.

ПРИМЕНЕНИЕ МЕБЕНДАЗОЛА ПРИ ЛЕЧЕНИИ ТРИХИНЕЛЛЕЗА У ЧЕЛОВЕКА

Т. Миттермайер и Р. Шпалдонова

Резюме. Описана эпидемия трихинеллеза в гг. Кошице и Рожнява в Словакии в декабре 1976 г. — январе 1977 г. Причиной эпидемии являлось поедание неосмотренного мяса дикого кабана. Заболевание преодолели 10 аппарентно инфицированных и 16 инпарентно инфицированных больных. Девять аппарентно инфицированных и одного инаппарентно инфицированного больного лечили мебендазолом в дозах 100—600 мг/день в ечение 6—10 дней. Клинический ход и результаты биоптического обследования показатаи что примененные дозы препарата не достаточны. Через два года после острого зарлжения повторялось лечение одного больного при помощи мебендазола в дозах 1000 мг/день в течение двух недель. Улучшение клинической картины и биоптическое обследование мышцев подтвердили наше предположение, что при лечении острого трихинеллеза нужно применять высокие дозы мебендазола.

REFERENCES

CAMPBELL W. C., Effect of thiabendazole upon infections of *Trichinella spiralis* in mice and upon certain other helminthiases. J. Parasitol. (Suppl.) 47: 37, 1961.

—, Antiinflammatory and analgesic properties of thiabendazole. Amer. J. med. Ass. 216: 2143, 1971.

—, CUCKLER A. C., The chemotherapy of experimental trichinosis in swine. J. Parasitol. 48: 28—29, 1962.

DE NOLLIN S., BORGERS M., VANPARIJS O., VAN DEN BOSCHE H., Effect of mebendazole on the encysted phase of *Trichinella spiralis* in the rat: an electron-microscope study. Parasitology 69: 55—62, 1974.

KEAN B. H., HOSKINS D. W., Treatment of trichinosis with thiabendazole. A preliminary report. Amer. J. med. Ass. 190: 852—853, 1964.

MITTERMAYER T., Problems of trichinellosis in eastern Slovakia. Prakt. Lék. (Praha) 53: 15—18, 1973. (In Slovak.)

—, CHROUST K., DEDINA L., ŠIMUNOVÁ M., Contribution to the clinic and therapy of trichinellosis treated with thiabendazole and mebendazole. Čas. Lék. čes. 117: 1053—1056, 1978. (In Slovak.)

—, CÍSÁROVÁ A., ČARNICKÁ A., MAGYAR B., MALOVESKÁ M., SCHRETER I., Cases of an acute trichinellosis with a neurological and mental symptomatology. Čas. Lék. čes. 118: 1175—1179, 1979. (In Slovak.)

PEREVERZEVA E. V., OZERETSKOVSKAYA T. N., VERETENNIKOVA N. L., Efficacy of carbamate benzimidazole derivatives and morphological changes in parasite and host muscle tissue in experimental trichinellosis. Proceedings of the Fourth Internat. Conference on Trichinellosis, August 26—28, Poznań, Poland. University Press of New England (Hanover, New Hampshire): 419—436, 1976.

SONNET J. J., THIENPONT D., The treatment of trichinosis with mebendazole. Acta Clinica Belgica 32: 297—302, 1977.

STONE O. J., STONE C. T., MULLINS J. F., Thiabendazole probable cure for trichinosis. Amer. J. med. Ass. 187: 536—538, 1964.

ŠPALDONOVÁ R., Influence of the intensity of the infective process in experimental trichinellosis. Doctor thesis. Helminth. instit. SAV, Košice, 1973.

—, ČORBA J., Studies on the effectivity of anthelminthics and their combination with immunosuppressives for *Trichinella spiralis*. Closing report. Helminthol. inst. SAV, Košice, 1977. (In Slovak).

—, TOMAŠOVIČOVÁ O., ČORBA J., The influence of mebendazole on the course of *Trichinella spiralis* infection in mice. Proceedings of the Third internat. Congress of Parasitology, Munich 25—31 August 1974. Vol. 2: 675—676, 1974.

THIENPONT D., VANPARIJS O., VANDESTEENE R., Anthelminthic and histopathological effects of mebendazole on *Trichinella spiralis* in the rat. In: Ch. W. Kim (Ed.): Trichinellosis, State University of New York, Sony Brook, pp. 515—527, 1974.

VUJEŠEVIĆ M., KOSTIĆ A., LAVIĆ R., ŽERJAV S., Mebendazole (Vermox) in the treatment of *Trichinella spiralis* infections. VII. Internat. Congress of Infectious and Parasitic Diseases. Varna — 2.—6. October 1978. Abstracts: 213—216, 1978.

Received 20 February 1980.

T. M., Kupeckého 33,
040 00 Košice, ČSSR