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## The efficacy of amoscanate (C9333-Go/CGP 4540) on filarial infections of *Mastomys natalensis*<sup>1</sup>

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In experimental investigations amoscanate (C9333-Go/CGP 4540), 4-isothiocyanato-4'-nitrodiphenylamine, was found to possess activity against several intestinal nematodes in mice, against schistosomes in various hosts and against three filarial species, *Litomosoides carinii*, *Dipetalonema viteae* and *Brugia pahangi* in *Meriones unguiculatus* (Striebel, 1976, 1978; Saz et al., 1977).

The present study concerns comparative investigations on the filaricidal activity of amoscanate in various formulations in *L. carinii*, *D. viteae*, *B. malayi* (subperiodic) and *B. pahangi* infected *Mastomys natalensis* (strain GRA Giessen). The animals were infected as reported previously (Lämmler et al., 1968; Sängler and Lämmler, 1979a, b) and were treated orally with single daily doses of amoscanate on five consecutive days. In the course of the experiment the microfilaraemia was determined regularly until the animals were necropsied 42 days after start of treatment.

The oral treatment with the various formulations of amoscanate revealed good activity of the drug against the cavity- and lymphatic-dwelling filariae used in the study, but lower efficacy against the tissue-dwelling filaria *D. viteae*. The detailed results are summarized in Table 1.

Oral administration of the micronized aqueous suspension lead to minimum effective doses (MED) of  $5 \times 25$  mg,  $5 \times 50$  mg,  $5 \times 12.5$  mg and  $5 \times 25$  mg/kg against microfilariae (MIF) of *L. carinii*, *D. viteae*, *B. malayi* and *B. pahangi*, respectively. Similar results could be achieved for the minimum curative doses (MCD) against microfilariae and adult parasites, determined 42 days after start of treatment. An oily suspension of amoscanate was apparently more effective, at least in *L. carinii* and *B. malayi* infected animals. The minimum effective dose against microfilariae was found to be half of the dose, which was necessary

<sup>1</sup> This investigation received financial support from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

Table 1. Chemotherapeutic activity of amoscanate on experimental filarial infections of *Mastomys natalensis*

Dose	Daily doses of amoscanate (mg/kg per os) on five consecutive days											
	Aqueous suspension 7.5%		Formulated aqueous suspension (syrup) 5%		Oily suspension 25%		Cremophor solution					
Median particle size ( $\mu\text{m}$ )	1.57		2.49		3.0		0					
Filaria sp.	L. car.	D. vit.	B. mal.	B. pah.	L. car.	D. vit.	B. mal.	L. car.	D. vit.	B. mal.	L. car.	D. vit.
MED (MIF) <sup>1</sup>	25	50	12.5	25	12.5	–	12.5	12.5	50	6.25	25	–
MCD (MIF) <sup>2</sup>	25	100	12.5	25	25	–	25	25	–	12.5	25	–
MCD (MAF/♀♀) <sup>2</sup>	25	100	25	25	25	–	>25	25	50	12.5	25	–
MCD (MAF/♀♀♂♂)	25	100	25	25	25	–	>25	25	50	12.5	25	–

<sup>1</sup> MED: Minimum effective dose = 95% reduction of microfilariae (MIF) 3, 7 or 14 days after start of treatment

<sup>2</sup> MCD: Minimum curative dose = 95% reduction of microfilariae (MIF) or macrofilariae (MAF) at the date of necropsy 42 days after start of treatment

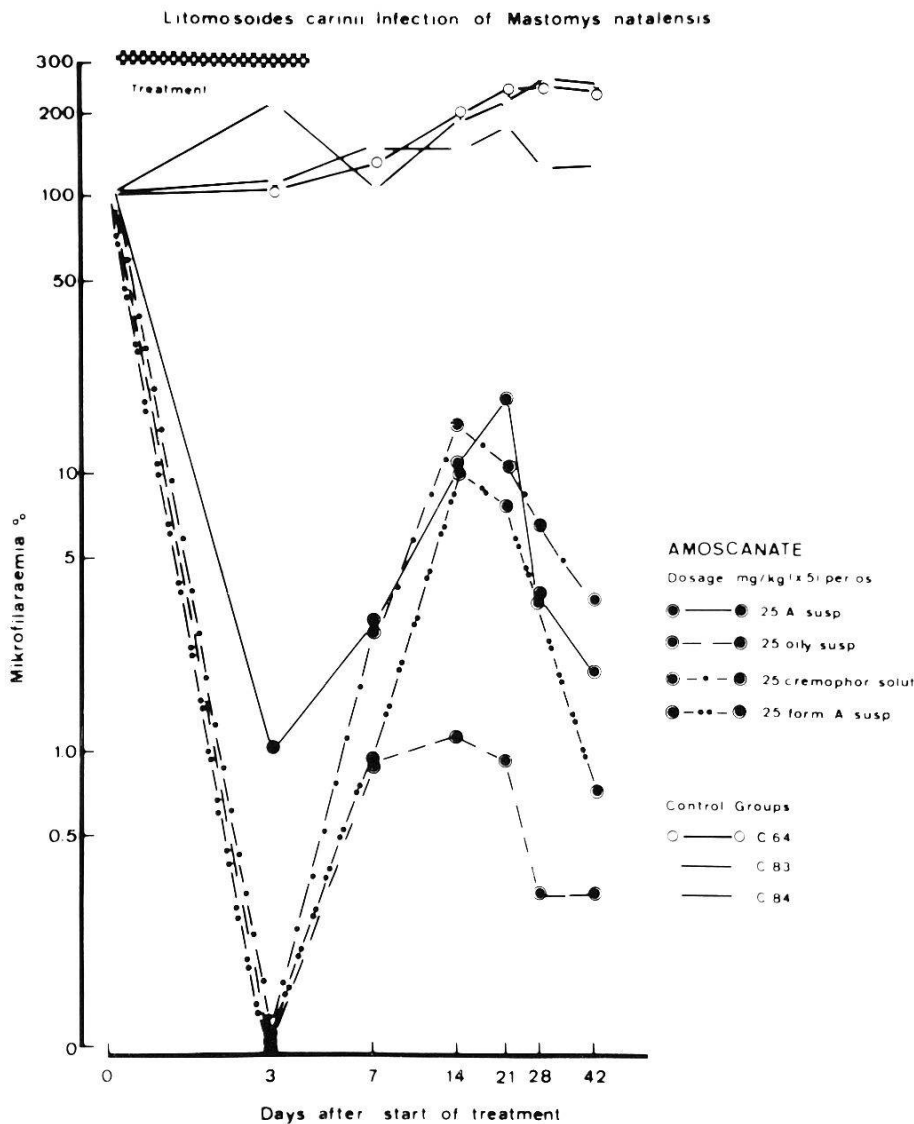


Fig. 1. Mikrofilariæmia in *L. carinii* infected *M. natalensis* after treatment with different formulations of amoscanate.

using the aqueous suspension of amoscanate. The latter results correspond to the findings of Striebel (1978) in *L. carinii* infected jirds.

A cremophor solution as well as a formulated aqueous suspension (syrup) of the drug showed similar activities to the micronized suspension in the case of *L. carinii* infection. However, the MED and MCD could not be fulfilled in the *D. viteae* infected animals; the efficacy was to less.

The effect of amoscanate in various formulations on the course of mikrofilariæmia was studied in *L. carinii* infected *M. natalensis* (Fig. 1). The mikrofilariæmia decreased rapidly. Three days after start of treatment, a reduction of the mikrofilarial counts of 99 to 100% could be observed. Between 14 and 21 days after drug administration a slight and transient reincrease occurred. At the date of necropsy, 42 days after start of treatment, the mikrofilariæmia was reduced at 96 to 99.7%. No living worms could be recovered from the pleural cavities of the host. Observations made after treatment of *B. pahangi* infected

jirds (Saz et al., 1977), which showed a longer persistence of living motile worms than in the present study might be dependent on the dosage and the single dose of short term administration using a different host. More informations on the time course of death and encapsulation of adult worms as well as on a reason for the persistently decreased microfilaraemia could be achieved in an additional experiment. Several groups of *M. natalensis* infected with 40 third-stage larvae of *L. carinii* were dissected 7, 14, 21, 28 and 42 days after oral treatment with  $5 \times 25$  mg/kg of the micronized aqueous suspension of amoscanate. An analysis of the embryogram (Wegerhof et al., 1979), showed, that amoscanate possesses an embryostatic effect, which is apparently especially directed to the early embryonic stages, i.e. 2- to 4-cell stages, morula stages and up to "horse shoe" stages. Increased rates of pathologically altered intrauterine microfilariae appeared later than 14 days after start of treatment. Encapsulation of adult worms in the pleural cavities increased gradually, but total encapsulation of all parasites occurred later than 28 days after start of treatment.

The results of this study demonstrate the altogether good filaricidal activity of amoscanate against microfilariae and adult parasites, but also a different efficacy in the same host against different filarial species. The drug proved to be most effective against the lymphatic-dwelling filaria *B. malayi* using the micronized aqueous and an oily suspension. Good activity could be observed also against *L. carinii* and *B. pahangi* whereas *D. viteae* was less affected.

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