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Antifilarial activity of mebendazole and flubendazole on *Breinlia booliati*

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Mebendazole (methyl 5-benzoylbenzimidazole-2-carbamate) has been found to be an effective anthelmintic against trichurids, ascarids and hookworms (CHAVARRIA *et al.*, 1973; HUTCHISON *et al.*, 1975). Although DUKE (1974) found it ineffective against *Onchocerca volvulus* in a chimpanzee, BERNBERG *et al.* (1979) showed it had microfilaricidal properties against *Dipetalonema perstans* when combined with levamisole. Furthermore, DENHAM *et al.* (1978) found it to be a potent filaricide against *Brugia pahangi* infection of cats and jirds when administered parenterally. Recently, too, the p-fluor analogue of mebendazole, flubendazole (methyl [5-(4-fluoro-benzoyl)-1-H-benzimidazole-2-yl] carbamate) was reported to be macrofilaricidal but not microfilaricidal against *B. pahangi* in jirds and cats (DENHAM *et al.*, 1979). The filaricidal properties of mebendazole and flubendazole were evaluated in this study in white rats infected with *Breinlia booliati*.

Materials and Methods

Breinlia booliati infection, originally from a naturally infected *Rattus sabanus* was passaged and maintained in white rats through syringe inoculation of infective larvae. 15 infected white rats with moderately high microfilaraemia were randomly assigned into three groups of five animals each. Mebendazole and flubendazole, kindly supplied by Janssen Pharmaceutica through the courtesy of Dr. Hugo Van den Bossche, was suspended in 1% Tween 80 in distilled water (DENHAM *et al.*, 1978) and given subcutaneously. The control group was given only 1% Tween 80 in distilled water. The second group was given mebendazole 10 mg/kg daily × 5 days while the third group flubendazole 3 mg/kg daily × 5 days. Microfilarial counts were obtained before, daily during, and thence weekly after treatment. All animals were followed up for four weeks after treatment and then autopsied.

Results

Effect of mebendazole and flubendazole on adult worms (Table I).

In the mebendazole group given a total dose of 50 mg/kg each, 60% had only dead or calcified worms in the thoracic and peritoneal cavities. 40% had live worms and the mean recovery of live worms for the group was 1·2. In the flubendazole group given a total dose of 15 mg/kg each, all worms recovered were either dead or calcified. In the control group all animals had live worms with a mean worm recovery of 7.2.

Table I—Effect of subcutaneous mebendazole and flubendazole on adult worms in *Breinlia booliati* infected white rats

Drug regime	Animal No./Sex	Infective dose (No. L3)	Worms recovered 4 weeks post-treatment			
			Live worms			Calcified & dead worms
			Males	Females	Total	
Mebendazole	96 M	102	0	0	0	+
10 mg/kg × 5 days	150 M	99	2	3	5	−
	154 M	92	0	1	1	+
	155 F	110	0	0	0	+
	158 F	102	0	0	0	+
Flubendazole	151 F	96	0	0	0	+
3 mg/kg × 5 days	156 F	101	0	0	0	+
	159 M	88	0	0	0	+
	165 M	101	0	0	0	+
	173 F	106	0	0	0	+
Control	117 F	110	1	2	3	−
	129 M	96	3	2	5	+
	131 F	102	8	12	20	−
	138 M	100	0	1	1	−
	149 F	109	3	4	7	−

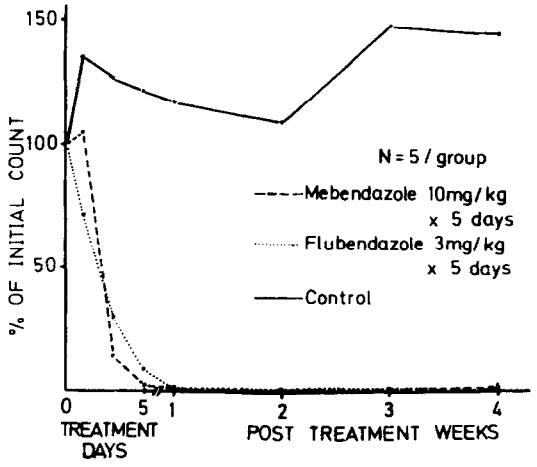

Fig. 1. Effect of subcutaneous mebendazole and flubendazole on mean microfilarial counts of *Breinlia booliati* infected rats.

Effect of mebendazole and flubendazole on microfilariae (Fig. 1).

In the control group there was a steady rise in mean microfilarial count and at autopsy it had risen to 144·1% of mean initial count (1123·6 microfilariae/20 mm^3). In both the mebendazole and flubendazole groups there were rapid drops in mean counts within the first few days of treatment, and at the last day of treatment it was 2·9% and 9·6% of initial counts (963·8 microfilariae/20 mm^3 and 1657·4 microfilariae/20 mm^3 respectively). At autopsy 60% of the animals in the mebendazole group were amicrofilaraemic and in the other two animals, final counts were very low. Mean final count was 1·5% of mean initial count. In the flubendazole group 80% of the animals were amicrofilaraemic while the count in the only positive animal was only 0·7% of initial count. The mean final count for the group was 0·2% of mean initial count.

Discussion

Both mebendazole and flubendazole are shown here to have significant filaricidal properties against *B. booliati* infection in white rats. Flubendazole appears to have greater macrofilaricidal as well as microfilaricidal effects than has mebendazole. Unlike their action in *Brugia pahangi* infection in jirds and cats, both drugs are active against the microfilariae and the adults of *Breinlia booliati*. This could be due to a difference in the susceptibility of *Brugia pahangi* and *Breinlia booliati* microfilariae to the drugs. In the treatment of human Malayan and bancroftian filariasis, side reactions due to diethylcarbamazine citrate could probably be caused mainly by the rapid, massive destruction of microfilariae, releasing antigenic/toxic products. The use of a mainly macrofilaricidal drug could probably achieve the final end result with fewer side reactions. It is therefore important to assess the action of mebendazole and flubendazole against the microfilariae and adults of *Brugia malayi*.

The mode of action of mebendazole and flubendazole against *Breinlia booliati* and *Brugia pahangi* is not known but is probably similar to that of mebendazole in *Ascaris suum* and *Syngamus trachea*, in which BORGERS *et al.* (1975) showed lethal damage to cytoplasmic microtubules of absorptive cells.

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