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FLUBENDAZOLE IN-FEED PREPARATION FOR PROPHYLAXIS OF EXPERIMENTAL LYMPHATIC FILARIASIS

by

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Using a laboratory model of a lymphatic dwelling filariid, *Brugia pahangi*, in the multimammate rats, *Mastomys natalensis*, our previous studies (2) have shown that micronized flubendazole (FBZ) when incorporated into the feed-pellets of these hosts at 500 ppm and fed *ad libitum* for seven days before infection and continued for another seven days post-infection offered complete protection against the infection. Studies were extended to evaluate this prophylactic efficacy of medicated feed containing FBZ at 100 ppm and 250 ppm and the results are reported.

Thirty-one random bred male multimammate rats, about three weeks old and weighing 55 to 83 g were used in four groups; the general protocol is outlined in Table 1. The animals of the groups A, B and C were fed on feed-pellets containing FBZ (micronized; mean particle size 2.7 μm) at different concentrations from day-0 through day-14 and returned to normal feed-pellets (unmedicated) from day-15 onwards. The amount of the medicated feed-pellets consumed daily by each rat was determined. All the animals of these three groups as also those of the group D, the latter receiving normal feed-pellets throughout the course of the experiment, received an infection inoculum of 200 infective larvae of *B. pahangi* s.c. in the groin region on day-7. Quantitation of microfilaraemia in the peripheral blood of the animals was done periodically and each time at 16.00 h of the day to avoid variations occurring due to cercadian rhythm of microfilaraemia. The animals of the groups A, B, C and D were sacrificed respectively at 38, 37, 33 and 26 weeks post-infection and their macrofilarial burden determined. The procedural details are given elsewhere (2).

TABLE 1
Experimental protocol

Groups	Multi-mammate rats (n)	Treatments		Necropsy
		Day-0 through day-14	Day-7	
A	8	Fed ad lib. on feed-pellets containing FBZ at 100 ppm	Infected with $200L_3$ of *B. pahangi*	38 weeks PI
B	9	Fed ad lib. on feed-pellets containing FBZ at 250 ppm	Infected with $200L_3$ of *B. pahangi*	37 weeks PI
C	8	Fed ad lib. on feed-pellets containing FBZ at 500 ppm	Infected with $200L_3$ of *B. pahangi*	33 weeks PI
D	6	Fed ad lib. on normal (unmedicated) feed-pellets	Infected with $200L_3$ of *B. pahangi*	26 weeks PI

Abbreviations used: PI = Post-infection, FBZ = Flubendazole.

The multimammate rats of the various groups consumed an average of nine g of medicated feed per animal daily during the two weeks feeding period. The absolute quantities of FBZ consumed by the animals of the three groups receiving feed-pellets containing the drug at various concentrations are shown in Table 2.

TABLE 2

Absolute amounts of FBZ consumed daily by multimammate rats of the three groups receiving medicated feed pellets

Groups	FBZ content in medicated feed pellets	Daily oral intake of absolute[+] amounts of FBZ (mg/kg)
A	100 ppm	10.84 - 16.36
B	250 ppm	27.11 - 40.91
C	500 ppm	54.22 - 81.82

[+] The calculations are based on the fact that each rat consumed an average of 9 g of medicated feed per day.

None of the animals of the medicated groups, A, B and C, showed microfilaria in the peripheral blood on 12, 14, 16, 18 and 26 weeks post-infection. Each animal of the unmedicated group D became microfilaraemic with an initial mean value of 36 microfilariae / 10 μl blood at 14 weeks post-infection and this rose to a mean value of 205 microfilariae / 10 μl blood at 26 weeks post-infection. Again, none of the animals of the medicated groups A, B and C harboured adult worms when necropsied on 38, 37 and 33 weeks post-infection, respectively while each animal of the group D harboured adults of *B. pahangi* and yielded an average of 24 (s.d.: 18.5) worms per animal on necropsy at 26 weeks post-infection.

The present results show irrevocably that FBZ given orally to multimammate rats at as low a dose rate as 11 mg/kg body weight daily for two weeks, by incorporating the drug in the normal feed, offered complete protection against *B. pahangi* infection. The larvicidal effect of FBZ on *B. pahangi* was ascertained earlier also (1, 3, 4) but the drug was used s.c. or i.p. Parenteral mode of drug administration, however, has poor acceptability for routine prophylactic use.

The microfilaricidal effect of diethylcarbamazine (DEC), the only drug used most widely against lymphatic filariasis, is well recognised and recently Ottesen (7) has compiled evidences in support of its macrofilaricidal activity in human lymphatic filariasis. If DEC also has larvicidal action in offering protection against lymphatic filariasis in man is not very clear and to quote Goodwin (5) « current evidence is inadequate to determine whether or not DEC is capable of prophylactic action ». Though the results from rodent model may be inadequate to extrapolate them directly to the infection in man, in experimental studies involving jirds and *B. pahangi* evidences were produced that while FBZ at 25 mg/kg given s.c. each day on day-3 to day-7 or day-10 to day-14 post-infection killed all the developmental stages of the filariid in the host (3), DEC at 300 mg/kg given i.p. each day on day-2 to day-6 or day-11 to day-15 post-infection only reduced the number of adult worms reaching maturity in the host (8). A complete prophylactic activity of FBZ given orally is confirmed in the present experiment. Apparently, a sustained level of plasma FBZ is required in achieving this activity as was shown earlier (2). The absorption of FBZ in the gastro-intestinal tract is limited because of its

poor solubility. Besides, a marked difference in the systemic absorption pattern of FBZ was observed in Wistar and multimammate rats; the former showed a superior absorption as adjudged by levels of plasma FBZ. In human subjects, a single oral dose of 2000 mg FBZ when given directly after a heavy meal was superior in achieving a much higher plasma FBZ level than when this dose was given before a meal (6).

The subperiodic brugian filariasis in man due to *B. malayi* infection in southeasth Asia is a zoonosis in that the monkeys (*Macaca* spp. and *Presbytis* spp.) and cats are known to serve as the reservoir hosts. A further evaluation of the prophylactic effect of FBZ medicated feed in endemic areas with a veiw to achieving a reduction in the incidence of *B. malayi* infection in these reservoir hosts may appear feasible and warrant some useful application of FBZ in the control of lymphatic filariasis.

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