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EFFECT OF IVERMECTIN ON TWO FILARIA-VECTOR PAIRS

Brugia malayi-Aedes aegypti; Litomosoides sigmodontis-Bdellonyssus bacoti[1]

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WITH THE TECHNICAL ASSISTANCE OF: S. PLATEAUX

SUMMARY

The effect of ivermectin was studied on two filaria-vector pairs, *Brugia malayi-Aedes aegypti* and *Litomosoides sigmodontis-Bdellonyssus bacoti.* The rodent hosts, respectively *Mastomys coucha* and *Meriones unguiculatus,* were treated with ivermectin doses of 0.05 mg/kg, or 0.2 mg/kg or 2 mg/kg. Batches of vectors were fed on rodents, infected or not, treated or not, from H7 to D43 post-ivermectin. Vector survival was observed and dissections were performed to study the filarial development.

It appears that ivermectin has no systemic effect on vectors, or very little. The drug acts on transmission because it affects the microfilariae. Transmission of *L. sigmodontis* is blocked because microfilariae are eliminated from the blood. Transmission of *B. malayi* is blocked although microfilaremia remains present at a low level. Two particular features are observed: microfilariae are hyper-ingested, but they do not cross the stomach wall (in contrast, they cross at a high rate in the control batch of *Aedes,* due to the « stomach wall limitation »). These events might be explained by a muscular passivity of the microfilariae treated with ivermectin. Transmission of the two filarioid species is restored normally about D25-40 post ivermectin because a new population of microfilariae has appeared.

These ivermectin experiments emphasize the diversity and complexity of two important phases of the filarial cycle in the vector: the ingestion of microfilariae and the passage through the stomach wall.

RÉSUMÉ : **Effet de l'ivermectine chez deux couples filaires-vecteurs : Brugia malayi-Aedes aegypti; Litomosoides sigmodontis-Bdellonyssus bacoti.**

L'action de l'ivermectine est étudiée chez deux couples filaire-vecteur, *Brugia malayi-Aedes aegypti* et *Litomosoides sigmodontis-Bdellonyssus bacoti.* Les rongeurs hôtes, respectivement *Mastomys coucha* et *Meriones unguiculatus,* sont traités aux doses de 0,05, ou 0,2 ou 2 mg/kg. Des lots de vecteurs sont gorgés sur des rongeurs parasités ou non, traités ou non, à différents temps post-ivermectine afin de suivre l'effet de la drogue pendant 30-40 jours. La survie des vecteurs et le déroulement du cycle de la filaire sont observés.

L'effet systémique de l'ivermectine sur ces vecteurs est nul ou négligeable. L'effet sur la transmission est dû à son action sur les microfilaires. Avec *L. sigmodontis,* la transmission est interrompue parce que la microfilarémie est annulée. Avec *B. malayi,* la microfilarémie diminue mais reste positive. Une sur-ingestion des microfilaires est observée, mais la transmission est interrompue car les microfilaires sont incapables de traverser la paroi stomacale du vecteur (chez le témoin, elles traversent à un taux élevé à cause de la « limitation stomacale »). Ces deux particularités s'expliquent vraisemblablement par une inertie musculaire des microfilaires due à l'ivermectine. Chez les deux couples filaire-vecteur, la transmission reprend normalement 25-40 jours après le traitement car une nouvelle population de microfilaires apparaît.

Cette analyse des modalités de la transmission après traitement par ivermectine confirme à nouveau la diversité et la complexité des mécanismes mis à jeu à deux moments essentiels du cycle : l'ingestion des microfilaires et la traversée de la paroi stomacale.

INTRODUCTION

The transmission of a filarial worm from an infected vertebrate to an uninfected one requires a combination of phenomena: ingestion of microfilariae by the vector, migration through the vector stomach wall, larval development, vector survival and filarial inoculation.

The goal of this study is to evaluate the effects of ivermectin on two filaria-vector pairs *Brugia malayi-Aedes aegypti* and *Litomosoides sigmodontis-Bdellonyssus bacoti,* and to try to define what are the steps of the cycle which are affected by the treatment. This study is particularly concerned with the weak points of the cycle during the development of the filaria in the vectors which are: (1) ingestion of microfilariae (Petit, 1978, 1985; Dickerson *et al.,* 1989) and (2) passage of microfilariae through the

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stomach wall of the vector (Bain, 1971; Brengues et Bain, 1972; Chabaud *et al.*, 1986).

General methods

Ivermectin (Ivomec bv® for veterinary use, Merck, Sharp and Dohme) was administrated by subcutaneous injection after dilution in propylen glycol. The control rodents received the solvant alone.

Vectors took blood meals at 14-15 hours. Prior to each experiment the microfilaremia of rodents was evaluated from 10 mm^3 of blood taken from the retro-orbital sinus. Microfilariae were counted in Giemsa stained thick blood smears.

Dissection of vectors was done in RPMI/20 % of new born-calf serum.

I — PAIR *BRUGIA MALAYI-AEDES AEGYPTI*

Material and methods

a — *Biological material*

The subperiodic strain of *B. malayi* was maintained in *Mastomys coucha*. The experimental vector was *A. aegypti*, Liverpool strain (isolated by McDonald, 1963). In order to obtain homogeneous breeding, eggs were hatched in hay water and the density was maintained at 200 larvae per liter; adults were obtained after 7/8 days and were used at the age of 5/6 days for the various experiments.

Mosquitoes were maintained 11 days subsequent to the infective feed in order to count the filarial larvae (L3). Some mosquitoes were dissected 17 hours after the blood meal. For each *Aedes*, microfilariae were counted separately in the stomach and in the rest of the abdomen and the thorax; this established the total number of ingested microfilariae (MfI) and the number of microfilariae which had passed through the stomach wall (MfP).

b — *Ivermectin (Iv) doses*

A preliminary experiment was done to define the effect of a high dose (5 mg/kg) on microfilaremia and vectors. The microfilaremia reached 25 % of initial value at 8 days (D8). It remained very low from day 21 to day 43. About twenty *Aedes* were fed 7 hours after treatment; most were unable to fly 17 hours after the blood meal. This dose was considered too high to allow a proper analysis of *B. malayi* development in the vector. The doses of 0.2 mg/kg and 2 mg/kg was then chosen.

c — *Experimental protocol*

Four groups of rodents (*M. coucha)* were used:

1 — infected and treated rodents: three at 0.2 mg/kg Iv (Nos. 5, 6, 7), one at 2 mg/kg Iv (No. 8),

2 — infected and untreated rodents: four (Nos. 1, 2, 3, 4),

3 — uninfected and treated rodents: one at 0.2 mg/kg Iv and one at 2 mg/kg Iv,

4 — uninfected and untreated rodent: one.

For each group and each dose, one rodent was chosen for *Aedes* blood meals (Nos. 1, 5, 8 and the 3 uninfected). Following a previous study by Chandre (1990) the choice of the infected untreated rodent was done taking into account the fact that the proportion of microfilariae escaping from the *A. aegypti* stomach increases when the number of ingested microfilariae decreases (« phenomenon of stomach wall limitation », Bain, 1971). Thus, it was ensured that the microfilariae of the untreated rodent was low, at a value similar to the value of the microfilaremia in the rodents after treatment. The blood meals were done at H7, H55, D8, D15, D21, D28, D35 and D43 post-ivermectin. For a given time, batches of *Aedes* were taken from the same larval breeding pool and the blood meals were done simultaneously for the different doses and the control. Forty eight batches of about 73 females each were used for the complete study.

Results

a — *Mortality of* A. aegypti *11 days after treatment (Table I)*

The dead females were counted and discarded daily. In most cases, mortality was the same in the batches feeding on treated and untreated rodents (< 9 %). A significant mortality was observed only with an ivermectin dose of 2 mg/kg : at H7, for rodents infected or not (respectively 33 % and 24 %) and at H55 only for infected rodents (14 %).

Table I. — *Mortality of* A. aegypti: *comparison of the cumulative percentages 11 days after the blood meal on* M. coucha *(infected or not, treated or not) according to the time post-ivermectin.*

The values in bold type indicate the mortalities significantly higher than those of the controls; H7 to D43: time after injection of ivermectin in hours (H) or days (D); Iv: dose of ivermectin in mg/kg.

Rodent	Iv	H7	H55	D8	D15	D21	D28	D35	D43
uninfected	0	0,0	1,8	3,6	0,8	1,2	0,0	2,2	1,4
	0,2	4,4	0,0	1,8	0,0	0,0	0,0	0,0	0,0
	2	**32,9**	8,8	1,8	1,1	0,0	1,2	1,1	1,7
infected	0	2,0	1,9	0,0	0,0	1,7	0,0	1,4	4,5
	0,2	2,1	0,0	0,0	1,1	5,9	0,0	1,1	1,8
	2	**23,9**	**14,3**	1,1	0,0	0,0	0,0	0,0	2,4

b — *Time course of microfilaremiae in* Mastomys coucha

The average time course of microfilariae is showed on Figure 1; the individual values are presented in *Table II.*

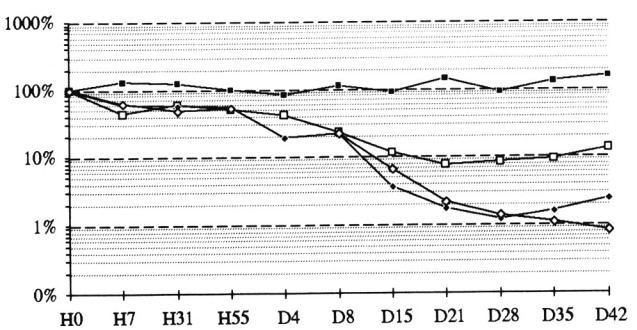

Fig. 1. — *B. malayi-M. coucha:* time course of microfilaremia expressed as percentage of initial microfilaremia (HO).
(■): Control; (□): 0.2 mg/kg; (◆): 2 mg/kg; (◇): 5 mg/kg.

TABLE II. — B. malayi-M. coucha: *time course of microfilaremias (Mf/10 mm³) in infected untreated and teated* M. coucha. *Individual values.*

T: time after injection of ivermectin in hours (H) or days (D); Iv: dose of ivermectin in mg/kg. The number of rodents in bold type indicate those used for the transmission experiment.

T	Iv								
	0				0,2			2	5
H0	34	37	78	500	43	36	273	489	363
H7	35	64	113	534	15	12	173	279	230
H31	40	37	125	584	24	30	108	331	174
H55	24	32	115	487	23	18	124	279	190
D4	9	46	78	418	22	14	94	94	-
D8	28	40	156	335	11	10	38	107	79
D15	45	24	45	558	9	3	14	3	24
D21	62	30	144	569	9	0	5	6	8
D28	36	12	91	482	10	0	3	5	5
D35	54	47	96	489	10	0	11	10	4
D42	79	40	136	585	12	1	22	19	3
Rodent n°	1	2	3	4	5	6	7	8	9

The microfilaremias remained constant, or increased, for the four infected control rodents (Nos. 1 to 4). The microfilaremias decreased from H7 and reached 25-30 % of the initial value at D8 with the five infected treated rodents (Nos. 5 to 9), whatever the dose of ivermectin. The microfilaremias remained at low level until D42; but, between D15 and D42, the reduction of microfilaremias was slightly more pronounced with ivermectin doses of 2 and 5 mg/kg (93-99 % of reduction, rodents Nos. 8 and 9) than with the dose of 0,2 mg/kg (87-92 % of reduction, rodents Nos. 5, 6, 7).

The microfilaremia fell to zero in one case only: rodent No. 6 with ivermectin dose of 0.2 mg/kg, between D21 and D35.

c — *Ingestion of microfilariae (Table III)*

This study was made with the rodent No. 5 treated at 0.2 mg/kg and the control rodent No. 1.

Results differed between the early phase (D1-D21) and the late phase (D21-after). During early phase, a much higher ingestion of microfilariae was observed with the treated rodent compared to the untreated one, although both had the same microfilaremia. The « ingestion efficiency », *i. e.* the ratio of microfilariae ingested/microfilaremia was about three times higher for *Aedes* batches fed on the control. During late phase, the « ingestion efficiency » was identical in both cases.

d — *Passage through the stomach wall (Table III)*

Due to the phenomenon of stomach wall limitation the effect of the treatment could be under-estimated if the number of ingested microfilariae is too low. However, the dose 0.2 mg/kg was clearly effective at H7 until D28. The passage through the stomach wall was restored almost to normal at D43.

TABLE III. — B. malayi-A. aegypti: *ingestion of microfilariae and passage through the stomach wall of vectors by microfilariae according to time post-ivermectin.*

T: time after injection of ivermectin in hours (H) or days (D); Iv: dose of ivermectin in mg/kg; Mf/mm³: microfilaremia of rodent in 10 mm³; MfI: mean number of ingested microfilariae per Aedes; *MfI/Mf: ratio ingested microfilariae to the microfilaremia; MfP: mean number of extrastomach microfilariae per* Aedes. *Each batches includes 25 to 30 Aedes.*

T	Iv	Mf/ mm³	Mf I	MfI/ Mf	Mf P
H7	0	3,5	5,3	1,5	2,7
	0,2	1,5	7,7	5,1	0,06
H55	0	2,4	4,1	1,7	1,5
	0,2	2,3	8,0	3,5	0,07
D8	0	2,8	8,1	2,9	1,6
	0,2	1,1	12,0	10,9	0,03
D21	0	6,2	12,2	2,0	3,7
	0,2	0,9	6,7	7,5	0,03
D28	0	3,6	17,3	4,8	3,3
	0,2	1,0	4,2	4,2	0,06
D43	0	7,9	27,1	3,4	3,4
	0.2	1,2	6,9	5,7	1,2

e — *Number of filarial larvae recovered (Table IV)*

Almost all larvae found at D11 were L3 larvae.

— The mean number of larvae fluctuated between 2.6 and 5.2 per *Aedes* fed on control rodent No. 1.

— No larvae were found in *Aedes* fed on rodent No. 5 treated at 0.2 mg/kg Iv, from H7 to D15. In fact, the few microfilariae which had passed through the midgut wall did not develop during this period. The first larvae appeared at D21. A normal amount of larvae were found in *Aedes* fed at D35 or later, indicating that the transmission had returned to normal.

— No larvae were found in *Aedes* fed on rodent No. 8 treated at 2 mg/kg Iv from H7 to D28. The first larvae appeared at D35. At D43, the transmission was normal, for the level of microfilaremia.

TABLE IV. — B. malayi-A. aegypti: *mean number of infective larvae per mosquito 11 days after blood meal on* M. coucha *according to post-ivermectin time.*

H7 to D43: time after injection of ivermectin in hours (H) or days (D); Iv: dose of ivermectin in mg/kg; Mf: microfilaremia of rodent in 10 mm³; L3: mean number of infective larvae per mosquito; n: number of Aedes.

Iv		H7	H55	D8	D15	D21	D28	D35	D43
0	Mf	35	24	28	45	62	36	54	79
	L3	2,6	2,8	3,6	5,2	3,6	3,1	2,5	4,3
	(n)	(50)	(52)	(69)	(73)	(57)	(66)	(72)	(62)
0,2	Mf	15	23	11	9	9	10	10	12
	L3	0,0	0,0	0,0	0,0	0,2	0,1	0,9	1,8
	(n)	(47)	(32)	(67)	(86)	(48)	(52)	(90)	(54)
2	Mf	279	279	107	3	6	5	10	19
	L3	0,0	0,0	0,0	0,0	0,0	0,0	0,2	1,1
	(n)	(67)	(53)	(90)	(86)	(82)	(82	(87	(81)

To summarize

Ivermectin did not affect the survival of *Aedes* at the dose of 0.2 mg/kg Iv but some mortality occurred at the dose of 2 mg/kg Iv; however, in this latter case, the lethal effect was not observed after H55. Ivermectin decreased microfilaremias but was unable to completely eradicate the microfilariae. It blocked the transmission from H7 although an hyper-ingestion occurred when microfilariae were taken up from the treated rodents. This interruption was due to the inhability of microfilariae to pass through the midgut wall of mosquitoes.

II — PAIR *LITOMOSOIDES SIGMODONTIS-BDELONYSSUS BACOTI*

Material and methods

a — *Biological material*

The experimental mammal host of *Litomosoides sigmodontis* (misnamed *L. carinii,* cf. Bain *et al.,* 1989) was the jird *Meriones unguiculatus.* The experimental vector is the mite *Bdellonyssus bacoti.* Breeding methods of this mite have been described by Diagne *et al.* (1990). Female mites only were used for the experiments. For each experiment, a batch of 75 females was poured on a given rodent. Fed females were collected on a water basin, placed under the rodent cage. They were kept in small tubes containing 20 mites each.

b — *Experimental protocol*

Four groups of jirds were used:

1 — infected treated rodents: one at 0.05 mg/kg (No. 1), six at 0.2 mg/kg (Nos. 2 to 7) and three at 2 mg/kg (Nos. 8 to 10),

2 — infected untreated rodents: three,

3 — uninfected treated rodents: one at 0.05 mg/kg, one at 0.2 mg/kg and one at 2 mg/kg,

4. uninfected untreated rodent: one.

In each group and for each dose, one rodent was chosen for the mite blood meals (8 rodents in total). The blood meals were done at H7, H31, H55, D4, D8, D16 and D29 post-ivermectin. Fifty-six batches of 75 mites were used for the complete study.

RESULTS

a — *Feeding capacity of* B. bacoti *and mortality during the blood meal*

An average of 42.4 mites per batch were engorged on rodents, treated or not. A low percentage of mites died during the blood meal, not related to the ivermectin doses.

b — *Mortality of* B. bacoti *11 days after bloodmeal*

The dead mites were counted daily, and not removed from the tubes. The percentage of dead mites was similar in treated and untreated batches, with an average of 18 % overall (extremes: 3 %-58 %).

c — *Fecundity of* B. bacoti

The protonymphs were counted at D11. Their mean numbers per female mite did not vary in the different batches; these means were 6.7, 7.2, 6.7 and 6.2 respectively for the batches fed on the controls, on the rodents treated at 0.05 mg/kg Iv, or 0.2 mg/kg, or 2 mg/kg.

d — *Time course of microfilaremia in* Meriones unguiculatus *(Fig. 2)*

The mean microfilaremia of the three infected but untreated controls remained stable from DO to D42 and was about 2.400 Mf/10 mm³.

The mean pretreatment microfilaremias in the 10 treated rodents were 1,860 Mf/10 mm³ for the rodent No. 1, 5,250 Mf/10 mm³ for Nos. 2 to 7, and 6,910 for Nos. 8 to 10. The mean microfilaremias were reduced to more than 99 % from H7, irrespective of the ivermectin doses. In all cases, microfilaremias fell to zero, from H55 generally. Positive microfilaremias reappeared in all rodents, and more or less rapidly according to the ivermectin dose: on D8 for No. 1 treated at 0.05 mg/kg, D16 for No. 2 to 7 treated at 0.2 mg/kg, D29 for Nos. 8 to 10 treated at 2 mg/kg. Microfilaremias did not reach the pretreatment values at D42: 870 Mf/10 mm³ for No. 1, 950 Mf/10 mm³ for Nos. 2 to 7, and 15 Mf/10³ for Nos. 8 to 10.

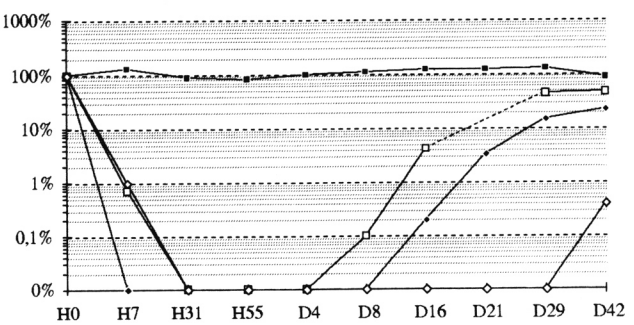

Fig. 2. — *L. sigmodontis-M. unguiculatus*: time course of microfilaremia expressed as percentage of initial microfilaremia (HO).

(■): Control; (□): 0.05 mg/kg; (◆): 0.2 mg/kg; (◇): 2 mg/kg.

e — *Number of filarial larvae recovered*

The mean numbers of L3 larvae per mite fluctuated from 1.0 to 3.9 L3 in the batches fed on the untreated rodent, and these figures followed the fluctuations of its microfilaremia (1,850 to 5,580 Mf/10 mm³). These mean L3 values were in accord with those from Diagne *et al.* (1900).

No L3 larvae were recovered from H7 to J16 post-ivermectin in the mite batches fed on treated infected rodents, whatever the ivermectin doses. Transmission was

restored at D29 for 0.05 and 0.2 mg/kg Iv, with respective means of 1.2 and 0.6 L3 per mite after feeding on microfilaremias of 790 et 1,050 Mf/10 mm³; these L3 values were in accord with dose from Diagne *et al.* (1990). Transmission was not restored at D29 with the rodent treated at 2 mg/kg Iv and with a very low microfilaremia (12 Mf/10 mm³).

To summarize

Ivermectin had no effect on the feeding, survival and fecundity of the female *B. bacoti.*

The mite vectorial capacity depended strictly upon the microfilarial density in the jird: transmission, which was temporarily blocked because microfilariae were eliminated from the blood, was restored to normal as soon as the microfilarial density was sufficient.

DISCUSSION AND CONCLUSION

In the two pairs of filaria-vectors studied, ivermectin has little or no effect on the vector. The drug acts on the filarial transmission because it affects the microfilariae.

With *L. sigmodontis,* the microfilaremia drops down during the first hours following the treatment; this fits with the results of Soeffner and Wenk (1985), who show that it is caused by the accumulation of blood microfilariae in the deep organs, such as the spleen and the liver, in which they are destroyed over the next two days. The release of the uterine microfilariae is also interrupted temporarily by the paralyzing action of the drug on the female filariae (Zahner *et al.,* 1987; Rao *et al.,* 1990*a*). Later, the positive microfilaremias correspond to the recovery of microfilarial release by the female worms. These new microfilariae are not altered, as demonstrated by the transmission rate, which is normal *(Fig. 3A).*

With *B. malayi,* the ivermectin effect is more complex: transmission is blocked for several days although the microfilaremias, which decrease, generally remain present *(Fig. 3B).*

Rao *et al.* (1990*b*) have shown that *Aedes aegypti* ingest microfilariae, after the ivermectin treatment, but that no larval development occurs. Our experiments demonstrate 1) an hyper-ingestion of the microfilariae by the mosquitoes fed on the treated rodents, 2) the inability of these ingested microfilariae to pass through the stomach wall of the vector. These two phenomena may be explained by an ivermectin induced inhibition of the neuro-muscular coordination in the microfilariae: these passive microfilariae might be drawn up more easily by the vector, but they cannot cross the barrier of the stomach epithelium. The hyper-ingestion in *B. malayi-A. aegypti* may be compared to the hypo-ingestion observed after treatment of *Onchocerca volvulus* in black flies (Prod'hon *et al.,*

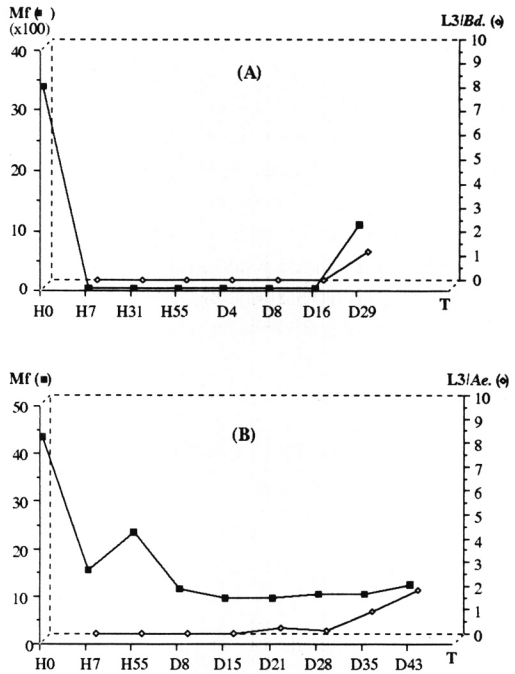

FIG. 3. — Relationship between microfilaremias of treated rodents with 0.2 mg/kg ivermectin and the mean number of infective larvae per vector.

A: *Litomosoides sigmodontis.* B: *Brugia malayi.* T: time after injection of ivermectin in hours (H) or days (D); Mf: microfilaremia of rodent per 10 mm³; L3/*Bd.,* L3/*Ae.*: mean number of infective larvae per vector.

1987); in that case, the surviving microfilariae are found deeper in the skin (Jurgens and Schulz-key, 1990) because they are unable to maintain themselves in the peripheral lymphatic vessels, and so are passively drained with the lymph into the deep lymphatic vessels (Vuong *et al.,* 1992).

The *B. malayi* transmission, with an ivermectin dose of 0.2 mg/kg, is recovered at low level at D21-28, then normally at D35, although the microfilaremia is not increased. This suggests that the release of microfilariae from the female filariae is recovered after D21, but microfilaremia remains constant because an equilibrium is created between the progressive destruction of the previous microfilariae and the release of the new microfilariae. About one month after treatment, most of the microfilariae are new, the transmission is recovered, with an excellent rate of development due to the phenomenon of stomach wall limitation. A similar event occurs in blackflies transmitting *O. volvulus* in the African Savanna; this explains why ivermectin treatment has not been able to block the transmission in that region (Remme *et al.,* 1990).

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