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EFFICACY OF IVERMECTIN AGAINST THE BLOODSUCKING INSECT, *RHODNIUS PROLIXUS* (HEMIPTERA, TRIATOMINAE)

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Ivermectin (0.2 mg/kg body weight) caused a high mortality in nymphs and adults of Rhodnius prolixus *following a single meal in mice sub-cutaneously injected with the drug. This effect was more evident in nymphs of 1st-and 2nd-instar than in older nymphs and adults.*

Third-instar nymphs presented a high mortality when fed on mice treated with ivermectin 24 and 48 hours previously, while mortality was significantly reduced in nymphs fed on mice treated 72 hours before. Surviving 3rd-instar nymphs did not molt.

When adult females were fed once on mice treated for 24 hours with ivermectin there was a considerable reduction in egg production. This inhibition was not reversed by a second feeding on normal mice.

We concluded that sub-lethal doses of ivermectin caused toxic effects interfering in the neuro-endocrine control of development and reproduction of this bloodsucking insect.

Key words: ivermectin – *Rhodnius prolixus* – Hemiptera – insect development – insect reproduction

Avermectins are antiparasitic substances produced by *Streptomyces avermitilis*, a new species of actinomycete (Burg et al., 1979). They have been isolated (Miller et al., 1979) and characterized as being a series of macrocyclic lactones (Albers-Schonberg et al., 1981). Among the chemical derivatives that have been prepared, 22, 23-dihydroavermectin-B1 (ivermectin) was considered of special interest in terms of antiparasitic action. It consists of a least 80% of 22, 23-dihydroavermectin-B1a and a maximum of 20% of 22, 23-dihydroavermectin-B1b (Campbell et al., 1983).

The efficacy and safety of ivermectin was demonstrated by both its high activity at extremely low dosage against a wide variety of nematode and arthropod parasites (Benz & Ernst, 1979; Lee, Dooge & Preston, 1979; Ostlind, Citelli & Lang, 1979), and by the apparent lack of side effects in antihelmintic dosages of up to 30 times its effective dose (Campbell et al., 1983).

It has been reported that ivermectin increased the mortality of *Glossina palpalis palpalis* fed on treated goats with higher doses than that recommended for use as an antihelmintic (Disdelmans, Haeseleer & Mortelmans, 1983). Moreover, Langley & Roe (1984) showed the potential use of ivermectin as a control agent of *G. morsitans morsitans*.

The purpose of the present paper was to study the effects of ivermectin on the development and reproduction of the Chagas' disease vector, *Rhodnius prolixus*. We evaluated its effect on the mortality of nymphs and adults, and consequently on the surviving insects or on the production of eggs and their fertility. We also estimated the rate of ivermectin elimination from the mice circulatory system using the above biological parameters.

MATERIAL AND METHODS

Nymphs and adults of *Rhodnius prolixus* were used throughout this study. They were reared and maintained as previously described (Garcia, Azambuja & Contreras, 1984).

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Ivermectin administration: Commercially available 1% ivermectin for sub-cutaneous administration was used. Albino outbred mice, ranging from 18 to 22g, were sub-cutaneously injected with 0.2mg in 0.15M NaCl/kg body weight.

Insect feeding: Synchronised insects, with 15-20 days starvation, were allowed to feed for 30 minutes on mice previously inoculated with ivermectin at different intervals after the administration of the drug. Unfed insects were removed and discarded. Control groups of insects were fed on mice receiving an injection of 0.15M NaCl.

Biological parameters assayed: The number of molting, egg production, eclodibility and mortality were considered at intervals following feeding. Insects which survived to 10 days were considered to have fully recovered from any effects of the initial ingestion of ivermectin.

RESULTS

Effects of sub-cutaneous administration of ivermectin in mice on nymphs and adults: The effects of mortality on insects with a single feeding on mice injected with ivermectin (0.2 mg/kg body weight) 24 hours before insect feeding is shown in Table I. Control insects of each group had a maximum of 5% mortality (not shown). The mortality in all instar nymphs and adults was significantly increased when insects were fed on mice treated for 24 hours with ivermectin. Table I also showed that the effect of ivermectin on the mortality was more drastic in the 1st-and 2nd-instar nymphs than 4th-and 5th-instar. Mortality of adult insects was 50%. At dosages lower than 0.2 mg ivermectin/kg body weight the mortality in all group was significantly reduced (not shown). The insects with 12 hours of blood ingestion containing ivermectin initially became lethargic with progressive paralysis of locomotor muscles. Such insects generally died within 24 hours of treatment. Apparently other physiological parameters such as gut distension and urine elimination were unaffected by ivermectin treatment.

TABLE I

Mortality of nymphs and adults *R. prolixus* following a single blood meal in mice 24 hours after receiving ivermectin (0.2 mg/kg body weight)

Treated Insects*	Ingested blood (mg)	Acumulative Mortality (%)			
		Days after feeding			
		1	3	5	9
1st instar	2,9 ± 0,2	30	98	98	98
2nd instar	8,0 ± 0,8	25	75	90	90
3rd instar	22,0 ± 2,1	20	60	80	85
4th instar	76 ± 4,2	5	50	68	70
5th instar	161 ± 6,8	5	30	60	60
Adults	132 ± 4,1	5	40	50	50

*50 – 60 insects for each experimental group.

TABLE II

Mortality of 3rd-instar nymphs of *R. prolixus* fed a single blood meal taken from mice at various times after treatment with ivermectin (0.2 mg/kg)

Time after mice treatment (hours)	Number of Insects	Acumulative Mortality (%)				
		Days after feeding				
		1	3	5	7	9
24	50	30	70	85	90	90
48	55	20	35	45	58	80
72	60	5	15	20	30	35
Controls	50	0	0	0	0	0

These symptoms could appear up to several days later. However, after this time, the toxicity of ivermectin progressively declined and little mortality occurred five days after feeding.

In order to evaluate the mortality of insects fed on mice at different times after treatment with ivermectin the following experiment was performed. Nymphs of 3rd-instar were allowed to feed on mice at different intervals after receiving treatment with ivermectin 0.2 mg/kg body weight. The results summarized in Table II compare the mortality of nymphs fed on mice after 24, 48 and 72 hours injection of ivermectin. There was an elevated mortality for nymphs fed on 24

hour-treated mice up to five days after feeding. The group fed on 48 hour-treated mice presented a level of mortality which represented half of the mortality of the first group. However, in the group fed on 72 hour-treated mice the mortality was greatly reduced being 40%, nine days after feeding. From the 9th day on the mortality was minimal.

Effects of ivermectin molting and reproduction: To verify the effects of ivermectin on development and egg production of *R. prolixus* the following observations were carried out. Surviving both nymphs of 3rd-instar fed on mice treated with ivermectin (0.2 mg/kg body weight) and mated adult females fed on 24 hour-treated mice were followed to compute the number of molts and eggs layed, respectively. A significant and drastic reduction was observed with no molting occuring in surviving nymphs fed on mice treated with ivermectin 24 to 72 hours previously. These findings were observed up to 30 days after feeding. In contrast, control insects had initiated the ecdysis on day 13 and attained 100% of molting 16 days after feeding.

TABLE III

Egg production of *R. prolixus* fed on 24 hours– treated mice with ivermectin (0.2 mg/kg)

Group of Females	Number of Insects	Oviposition cycle	
		1st	2nd
Treated	18	1 egg/female	1.8 egg/female
Controls	17	7 egg/female	9 egg/female

The results presented in Table III show the reduction in number of eggs produced by females fed once on 24 hour-treated mice with ivermectin (0.2 mg/kg body weight). The decrease in egg production was maintained even in the 2nd oviposition cycle after the females had a new feeding on normal mice. However, the eclodibility recorded for both groups was 85%, i.e., ivermectin apparently did not alter the fertility of these females.

DISCUSSION

The mode of action of ivermectin as an antiparasitic agent is apparently to inhibit the mediation of neurotransmission by gamma aminobutyric acid (GABA) (Fritz et al., 1979; Campbell, 1981). Arthropods in particular, use GABA as a neurotransmitter. It is therefore probably that the paralyse and mortality induced by ivermectin in *Rhodnius* could be due to its direct action on the neuromuscular transmission.

The greater sensitivity of the 1st-instar nymphs to ivermectin compared to 4th-and 5th-instar and adults (Table I), is probably due to the higher percentage of fat body in the latter as the dosages are practically same. Langley & Roe (1984) pointed out that ivermectin being lipophilic would be removed effectively from the hemolymph into the fat body, thus decreasing its action in the larger insects.

Soll et al. (1984) showed that cattle tick are killed following ingestion of blood meal containing ivermectin, and *Ornithodoro savignyi* is paralysed by a dose of 0.2 mg/kg body weight which is effective from 12 hours up to seven days after treatment.

Langley & Roe (1984) demonstrated that the effects of ivermectin on *G.m. morsitans* females was significant after a single fed on blood from a horse receiving 0.4 mg/kg, twice the anthihelmintic dose, 24 hours previously. The authors estimated that the half-life of the drug in horse was 5-6 days. Our present findings using the dose of 0.2 mg ivermectin/kg body weight, showed, indeed, that the induction of mortality in 3rd-instar nymph was high when the insects fed on mice which had received ivermectin 48 hours previously. From this time on, the mortality was significantly reduced (Table II). However, perhaps the more important aspect of the ivermectin action on *Rhodnius* is its prolonged inhibition of molting. The surviving nymphs fed on 24 hour- to 48 hour-treated mice did not molt during at least the 30 days of the experiment. It should be emphasized here that this effect was also observed on insects fed on 72 hour-treated mice which caused only little mortality.

We also observed that ivermectin reduced drastically the production of eggs. The treated females were unable to reverse this effect even after feeding on normal mice (2nd oviposition cycle; Table III).

We suggest, based on the effect on molting and egg production, that ivermectin must cause some sub-lethal toxic effects which interfere with both neural and endocrine control of these two biological parameters.

RESUMO

A alimentação de ninfas e adultos de *Rhodnius prolixus* em camundongos tratados previamente com ivermectin (0,2 mg/kg peso corporal, via subcutânea) resultou em alta mortalidade dos insetos. Este efeito foi mais drástico em ninfas de 1º e 2º estádios.

Foi observado que as ninfas de 3º estádio alimentadas 24-48 horas após o tratamento dos camundongos demonstraram uma mortalidade maior do que os insetos alimentados 72 horas após o tratamento. Os insetos de 3º estádio sobreviventes aos tratamentos apresentaram uma inibição total das mudas.

Fêmeas adultas alimentadas em camundongos 24 horas após o tratamento com ivermectin demonstraram uma considerável redução na produção de ovos. Este efeito não foi revertido por uma posterior alimentação em camundongos normais.

Foi sugerido que dose subletal de ivermectin poderia interferir no controle neuro-endócrino do desenvolvimento e reprodução do inseto.

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