Systemic Activity of Ivermectin on the Human Body Louse (Anoplura: Pediculidae)

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J. Med. Entomol. 27(1): 72–75 (1990)

ABSTRACT Eighty-one to 100% of nymphs and females of the human body louse (*Pediculus humanus humanus*) that fed artificially on blood containing 2.5–10 ng ivermectin/ml died. The mortality of nymphs and female lice fed on rabbits treated with 200 μg/kg ivermectin was very high during the first two to three days, then declined sharply, reaching the level of the controls on day six. Nymphs were more sensitive than females. The average number of eggs laid by surviving females and the percentage that hatched from those eggs were lower than in controls.

KEY WORDS Insecta, Anoplura, *Pediculus humanus humanus*, systemic activity

IVERMECTIN is a derivative of the macrocyclic lactone avermectin B_1, a naturally occurring fermentation product isolated from the actinomycete *Streptomyces avermitilis*. It is anthelminthic, insecticidal, and acaricidal (for reviews, see Campbell 1985, Strong & Brown 1987).

The efficacy of ivermectin, administered at 200 μg/kg doses, against a variety of louse species has been studied in clinical trials on cows (Barth & Sutherland 1980, Barth & Preston 1985), pigs (Barth & Brokken 1980), buffaloes (Lau & Singh 1985), impalas (Horak et al. 1983), mules and white-tailed deer (Foreyt et al. 1986), and elephants (Karesh & Robinson 1985). However, the efficacy of ivermectin against arthropod parasites of man has not been investigated.

This study investigated the systemic activity of ivermectin on the human body louse *Pediculus humanus humanus* L., fed by an artificial feeding technique, and on laboratory animals inoculated with ivermectin.

Materials and Methods

Lice. Laboratory colonies of human body lice (*P. h. humanus*) were maintained at 30 ± 1°C and 70 ± 5% RH. Every other day, lice were placed on the shaved abdomen of a restrained rabbit and allowed to feed to satiety.

The artificial feeding apparatus for the lice consisted of a plastic beaker (3.2 cm diameter and 4.5 cm high) into which approximately 2 ml of lysed blood containing ivermectin at various concentrations was placed. The feeding chamber (2.5 cm diameter by 5.5 cm high) was first covered with nylon netting (1.5-mm mesh) and then with a silicon membrane held in place with rubber bands. The feeding chamber could be lowered into the plastic beaker to a level just beneath the level of solution in the beaker (approx. 2 mm). Petroleum jelly or Tanglefoot (Tanglefoot Company, Grand Rapids, Mich.) placed around the top of the feeding chamber prevented the lice from escaping. Forty lice (20 females and 20 nymphs) starved for 48 h, were placed on a 1-cm^2 patch of black corduroy, which was inserted into the feeding chamber. The whole apparatus was placed on a hot plate; the temperature on the membrane surface was maintained at 33 ± 2°C. The ambient temperature was 26–28°C and the relative humidity was 55 ± 5%. The lice were allowed to feed for 2 h in a dark room. They were then removed; those fully engorged were counted, placed on fresh pieces of corduroy, and incubated at 30 ± 1°C and 70 ± 5% RH. The mortality was estimated at 24 and 48 h.

The silicon membranes were placed according to a method described by Mumcuoglu & Galun (1987).

Solutions. Whole citrated human blood was frozen at −20°C and thawed on the day of use. Solutions of ivermectin were made up in propylene glycol (Sigma, St. Louis) and then diluted in the thawed blood to give final concentrations of 1.25, 2.5, 5, and 10 ng/ml. Controls had propylene glycol only. Experiments were replicated at least four times for each concentration.

Feeding of Lice. Six white New Zealand rabbits, each weighing between 2.2 and 3.1 kg, were injected subcutaneously with a solution of ivermectin in propylene glycol, 200 μg per kg of rabbit weight; the two controls were injected with 1 ml of propylene glycol. Preliminary studies showed that maximum efficacy of ivermectin was reached on the first day after inoculation.

Twenty-four hours after the ivermectin injection into the rabbit, 100 lice, 50 females and 50 nymphs,

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Table 1. Average percentage of mortality of human body lice fed on blood containing ivermectin

Ivermectin, ng/ml	Mean percentage mortality (n)	
	Nymphs	Females
0	9.9 (540)	3.8 (156)
1.25	30.3 (373)	12.3 (130)
2.5	92.5 (307)	81.4 (78)
5	94.8 (302)	85.5 (84)
10	99.3 (328)	100 (90)

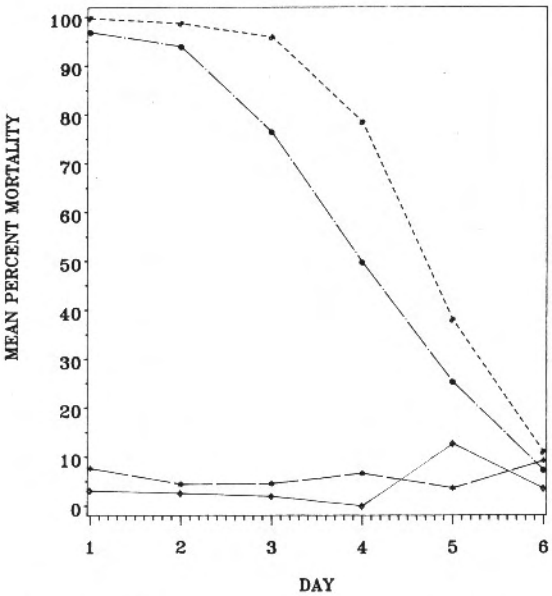

Fig. 1. Mean percentage of mortality of lice fed on rabbits 1–6 d after injection of 200 μg/kg ivermectin. (-----) Nymphs in the experimental group, (-·-·-) females in the experimental group, (——) nymphs in the control group, (– – –) females in the control group.

starved for 24 h, were placed on the shaved abdomen of the rabbit and allowed to feed for 1 h. Fully engorged lice were counted, removed to a fresh piece of corduroy, and maintained at optimal conditions. After 24 h, the percentage of mortality and number of eggs laid were recorded. The lice were then discarded, and the eggs were incubated under optimal conditions. Ten days later, the percentage of hatched was recorded. Fresh groups of lice were fed on these rabbits daily for 6 d.

Results

Artificial Feeding. According to the data presented in Table 1, nymphs were slightly more sensitive to ivermectin than females, although for both, the LD_{50} fell between 1.25–2.5 ng ivermectin/ml blood, and the LD_{95} between 5–10 ng/ml.

Rabbit Feeding. The mortality of nymphs and females fed on treated rabbits (200 μg/kg) was very

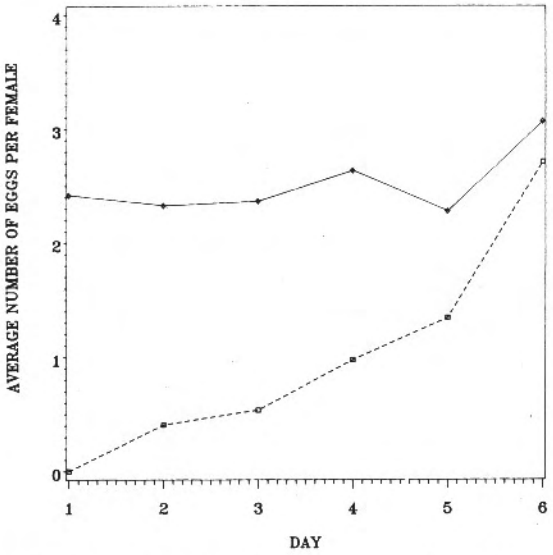

Fig. 2. Average number of eggs per female louse fed on rabbits 1–6 d after rabbits were injected with 200 μg/kg ivermectin. (– – –) Experimental group, (——)control group.

high during the first 2 or 3 d, then declined sharply, reaching the level of the controls on the sixth day (Fig. 1). Nymphs were more sensitive than females. Mortality of lice fed on control rabbits was usually <10%.

The average number of eggs laid per female is shown by treatment group over day in Fig. 2. The numbers in the treated group are consistently lower than those in the control group, but approach those of the control group on day 6. The slopes of the lines are different; whereas the line for the untreated group is nearly parallel to the day axis, indicating no particular relationship between mean number of eggs per female and day, the line of the treated group is a monotonically increasing function, indicating a decrease in the effect of treatment over day. These observations lead to the following analysis of covariance mode (Dixon et al. 1985):

$$\text{(I)}\quad E = \beta_0 + \gamma I + \beta_1(\text{DAY}\cdot I) + \beta_2[\text{DAY}(1 - I)] + \beta_3(\text{DAY}^2\cdot I) + \beta_4[\text{DAY}^2(1 - I)]$$

This model reduces to the following:

$$\text{(II)}\quad E = \beta_0 + \gamma + \beta_1\text{DAY} + \beta_3\text{DAY}^2 \text{ for treated}$$
$$E = \beta_0 + \beta_2\text{DAY} + \beta_4\text{DAY}^2 \text{ for control}$$

where E = average number of eggs per female; β_0 = general intercept; γ = treatment constant contribution; β_1 = coefficient of linear term for day for treated group; β_2 = coefficient of linear term for day for control group; β_3 = coefficient of squared term for day for treated group; β_4 = coefficient of squared term for day for control group; and I = an indicator variable which takes the value of 1 for treated and 0 for control.

The coefficient for linear terms for day in both groups and the coefficient for the squared term for

day in the control were not significant. The final model is $E = -0.10 + 0.07\ DAY^2$ for the treated group and $E = 2.51$ for the control group.

The R^2 associated with this model is 0.61. The P values for group effect and for DAY^2 in the treated group are both 0.0001. It can be seen that the final model is a straight line parallel to the day axis for the control group and a quadratic function for the treatment group. This is consistent with Fig. 2.

The average percentage that hatched from the eggs of surviving females was between 0 and 82% in the experimental group and between 76 and 97% in the control group. Controls had consistently higher rates of hatching than the treated females, but there was no strong pattern in either group. The mean daily percentage that hatched was compared for the two groups using the Wilcoxon Matched-pairs Signed-rank test. The two-sided test showed a significant difference between the two groups at the $P = 0.05$ level.

The feeding pattern of the lice on the treated and nontreated animals was virtually the same. This was also true for lice that engorged on treated and untreated blood.

Lice affected by feeding on treated animals or on blood containing ivermectin in an artificial feeding apparatus either died within 24 h or showed signs of intoxication within 24 h and died within 48 h. Lice remained fully engorged until death. They were lethargic and their mating behavior was affected.

Discussion

Horn flies, *Haematobia irritans* L., stable flies, *Stomoxys calcitrans* L., and tsetse flies (*Glossina* spp.) have been fed with blood containing various concentrations of ivermectin using artificial feeding techniques (Langley & Roe 1984, Miller et al. 1986). We found that the female body louse, *P. h. humanus*, fed artificially was as sensitive as horn flies, 10 times more sensitive than tsetse flies, and at least 20 times more sensitive than stable fly females.

Our results with artificial feeding indicate that unmetabolized ivermectin may be a systemic toxicant rather than a metabolite. This supports the observations of Nolan et al. (1981) on the action of ivermectin on ticks.

Therapeutic doses of 200 μg ivermectin/kg appear to be effective against all species of animal lice examined to date (see introduction). Our results with human body lice fed on treated rabbits confirm these observations. Although 200 μg/kg produced a high mortality in the lice population for 2–3 d, our results suggest that larger doses would be required to provide a high level of control for longer periods.

Differences in susceptibility between nymphs and adult females also have been observed in *Rhodnius prolixus* Stal (Azambuja et al. 1985). Differences have similarly been observed between male and female tsetse flies (Langley & Roe 1984) and between male and female horn and stable flies (Miller et al. 1986). Younger developmental stages were more sensitive than older ones in *Blatella germanica* L. (Cochran 1985), in *R. prolixus* (Azambuja et al. 1985) and in *Culex quinquefasciatus* Say (Suryanarayana Murty et al. 1987).

Pediculus h. humanus fed on rabbits that were treated with a standard dose of 200 μg ivermectin/kg were as sensitive to ivermectin as *Culicoides brevitarsis* Kieffer (Standfast et al. 1984) and *Psoroptes ovis* (Hering) (Meleney et al. 1982) but more sensitive than *Anopheles stephensi* Liston, *Aedes aegypti* (L.) and *C. quinquefasciatus* (Pampiglione et al. 1985), *S. calcitrans* and *H. irritans* (Miller et al. 1986), *Glossina palpalis* (Rob.-Desv.) (Distelmans et al. 1983, Langley & Roe 1984) and *Melophagus ovinus* L. (Guerrero Molina & Euzeby 1982).

The effect of a single injection of ivermectin (200 μg/kg) on heifers or calves lasted for 2–4 wk when tested on *P. ovis* (Guillot et al. 1986), *Sarcoptes scabiei* (L.) (Meleney et al. 1982), *Amblyomma americanum* (L.) (Lancaster et al. 1982) and *C. brevitarsis* (Standfast et al. 1984). Duration of the residual activity of ivermectin in rabbits was much shorter. Six days after ivermectin was injected into rabbits, no effect on louse mortality, oviposition, or percentage of hatched eggs was discerned. Perhaps this explains why rabbits infested with *P. ovis*, *P. cuniculi* and *S. scabiei* had to be treated twice (7-d interval) to achieve satisfactory results (Romero & Garcia Valenti 1984, Prosl & Kanout 1985, Wright & Riner 1985). It is possible that ivermectin is metabolized more quickly in rabbits than in cattle.

Ivermectin in the blood of rabbits or suspended in human blood in artificial feeding devices neither diminishes the attractiveness of the blood nor prevents engorgement by lice or other hematophagous insects (Standfast et al. 1984).

Ivermectin causes lice to remain fully engorged and lethargic. Tsetse flies that ingested a blood meal containing ivermectin became lethargic, showed reduced flight activity and progressive paralysis of locomotory muscles (Langley & Roe 1984), and died within 48 h. *Glossina* also remained distended with fluid, indicating problems with water balance (Distelmans et al. 1983).

Ivermectin affects the fecundity of most of the arthropod species that have been examined (Langley & Roe 1984, Cochran 1985, Guillot et al. 1986, Miller et al. 1986). Our results agree with those found for *Xenopsylla cheopis* (Rothschild) (Campbell 1986) and *G. palpalis* (Langley & Roe 1984) where reduction in the number of eggs laid was observed following sublethal doses.

We found that the percentage of hatched louse eggs was reduced after ingestion of blood containing ivermectin. A similar effect on the eggs of horn and stable flies (Miller et al. 1986) and of ticks (Nolan et al. 1981) has been reported.

Topical application of ivermectin is very effective against the cattle louse *Linognathus vituli* (L.) (Barth et al. 1986). Preliminary studies in our laboratory show that this compound is also active against human lice when used topically (K.Y.M., unpublished data). Today ivermectin is being administered orally to humans to combat *Onchocerca volvulus* infestation (Greene et al. 1985). This makes ivermectin a good candidate for a human pediculocide.

Acknowledgment

We thank Merck, Sharp & Dohme for providing the ivermectin powder used for this study.

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Received for publication 14 November 1988; accepted 5 April 1989.