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EFFICACY OF IVERMECTIN AGAINST NEMATODES INFECTING FIELD POPULATIONS OF SNOWSHOE HARES (*LEPUS AMERICANUS*) IN YUKON, CANADA

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ABSTRACT: From July 1990 to February 1991, nematode numbers in free-ranging snowshoe hares (*Lepus americanus*) at Kluane Lake, southwestern Yukon, Canada, were manipulated by subcutaneous injection (0.4 mg/kg) of ivermectin. Three field experiments were conducted to determine the degree of helminth loss associated with a single administration of ivermectin; the length of time that ivermectin was effective in reducing worm numbers; and the effect of repeated ivermectin administration in reducing worm numbers. Numbers of the nematodes, *Protostrongylus boughtoni* and *Nematodirus triangularis* were reduced by approximately 80% 2 wk after treatment with a single dose of ivermectin, and were still significantly lower than controls at 4 wk. However, beyond 2 wk, ivermectin did not affect the rate of acquisition of new worms of either species. All treated groups contained one or more hares in which numbers of *P. boughtoni* and *N. triangularis* were not reduced. In addition, ivermectin had no effect on numbers of *Trichuris leporis* or *Passalurus* sp. Overall, ivermectin was not as effective against the nematodes of free-ranging hares as has been reported for nematodes of domestic and laboratory animals.

Key words: Ivermectin, nematode, field manipulation, snowshoe hare, *Lepus americanus*, chemotherapy, free-ranging host, efficacy.

INTRODUCTION

For experimental field biologists, an effective, broad-spectrum anthelminthic could be useful in manipulative field experiments testing the influence of parasites on population dynamics of wild vertebrates. For example, Hudson (1986) and Hudson et al. (1992) used levamisole, administered in supplemental food, to treat free-ranging red grouse (*Lagopus lagopus scoticus*) against the nematode *Trichostrongylus tenuis*; treated populations had greater nesting success and decreased mortality. Administration of treated food, however, has two major disadvantages. It is impossible to know which animals have been treated, and what dosage of drug was ingested. In addition, the influence of the drug is confounded with the influence of the supplemental food. Where overall experimental protocols call for distinguishing the influences of food addition and of drug treatment, as in the Kluane project on snowshoe hares (Krebs et al., 1986, 1992), a different method of administering the anthelminthic is needed. We therefore designed this study to determine if injectable ivermectin (Campbell, 1989) could be used successfully to reduce numbers of nematodes in a field population of snowshoe hares (*Lepus americanus*).

Ivermectin was chosen because it is effective against a broad range of nematodes in domestic animals (Campbell, 1989), is relatively non-toxic (Lankas and Gordan, 1989), and has relatively long-lasting effects in treated animals (Campbell and Benz, 1984; Lo et al., 1985). In domestic laboratory rabbits, for example, high concentrations of ivermectin were sustained in tissues and body fluids for at least 13 days following injection (McKellar et al., 1992).

Our objectives were to determine the degree of worm loss associated with a single administration of ivermectin; the length of time that ivermectin was effective in reducing worm numbers; and the effect of repeated ivermectin administration in reducing worm numbers.

MATERIALS AND METHODS

Research was conducted in the boreal forest at Kluane Lake, Yukon Territory, Canada (61°01′N, 138°24′W). This area is described by Krebs et al. (1986, 1992). Hares were captured

with (20 cm × 20 cm × 60 cm) Tomahawk livetraps (National Live Trap Corporation, Tomahawk, Wisconsin, USA). The sex of each captured hare was determined, and each hare was also weighed and tagged in its right ear with a numbered monel size 3 eartag (National Band and Tag Company, Newport, Kentucky, USA). Hares were injected subcutaneously in the right hip with a 1.0% solution of ivermectin (Ivomec™ for swine, ASD AGVET, Merck Frosst, Rahway, New Jersey, USA) diluted in 100% propylene glycol, such that each hare received 0.4 mg/kg of ivermectin (McKellar et al., 1992). Each control hare was sham injected with 0.4 mg/kg of propylene glycol.

Trapped hares destined for necropsy were killed by cervical dislocation. The sex, weight, and eartag number of each collected hare were recorded at the time of its collection. Hares in this population lack stomach worms and ticks (J. R. Sovell and J. C. Holmes, unpubl.). Therefore, each collected hare was examined for intestinal nematodes and lungworms only. The small intestine and the large intestine and cecum each were flushed with tap water, opened, and scraped. The flushings and scrapings were washed through 850 μm and 250 μm sieves (VWR Scientific, West Chester, Pennsylvania, USA) for the small intestine, and 850 μm and 425 μm sieves for the large intestine and cecum. Material collected in each sieve was partitioned into petri dishes, diluted with tap water, and examined using a dissecting microscope. All nematodes were identified and counted (Skrjabin et al., 1960, 1974; Boev, 1984).

The trachea and lungs were removed intact; small pieces of tissue were removed from the tip of the apical, cardiac, and diaphragmatic lobes of each half of the lung; and the bronchi were flushed with tap water. The effluent was examined as above. The air tracts of both the flushed lung and the tissue pieces were opened with scissors and examined. All lungworms were removed and counted.

In August 1990, 18 hares were trapped on a 5.4 ha grid. Eight were examined for worm numbers present at the start of the experiment, and 10 were treated with a single dose of ivermectin. The 10 treated hares were kept in five pens (1.8 m × 4.6 m × 1.0 m), with one male and either one or two females in each pen. One treated hare escaped. The pens were constructed from chicken wire and the base of each wall was buried 15 cm into the ground. The hares were supplied ad libitum with rabbit chow (Shur-Gain, Edmonton, Alberta, Canada) once a day and with willow (*Salix glauca*), and bog birch (*Betula glandulosa*), in the morning and evening of each day. Infection from transmission of larval parasites in the environment was not possible in this group of penned hares. At 3 wk after treatment, the remaining nine treated hares from the holding pens were killed and the carcasses were stored at −20 C. At the same time, 10 hares which had not been treated or sham injected with propylene glycol, were trapped on the 5.4 ha grid, killed by cervical dislocation, and frozen. Lack of available pen space prevented us from maintaining untreated hares in pens during this experiment.

For experiment 1, 76 hares were trapped on the 5.4 ha grid in July 1990. Sixteen were killed and examined for parasites to assess numbers of worms present at the start of the experiment, 40 were treated with a single dose of ivermectin and released, the remaining 20 were sham-injected and released as untreated controls. Seven weeks later, 10 treated and eight control hares were retrapped, killed, and examined for nematodes.

For experiment 2, 31 hares were trapped on the 5.4 ha grid in July 1991; six were examined for numbers of worms present at the start of the experiment, 15 were treated and released, and 10 were sham-injected and released as untreated controls. At 2 wk post-treatment, six treated and five control hares, respectively were retrapped, killed, and examined for parasites. At 4 wk, seven treated and five control hares were retrapped, killed, and examined for parasites.

For experiment 3, we assessed the long-term effects of multiple treatments with ivermectin on subsequent numbers of nematodes. Two 13 ha grids were trapped at monthly intervals from May to September of 1990 and 1991, plus November 1990 and February 1991. Trap success was variable between months, and there was some immigration and emigration during this period. All captured hares were injected subcutaneously in the right hip with 0.4 mg/kg of ivermectin every time that they were trapped (McKellar et al., 1992). As a result, hares that remained faithful to the study area throughout the course of the experiment received several injections of ivermectin. In November 1991, all available hares were trapped, killed, and the carcasses frozen for later examination. Of the hares killed in November 1991, six had been trapped and treated three or four times during the summer of 1991, and they had received their last treatment a mean (±SD) of 12 (±4.7) wk previous to their collection. To assess the long-term influence of repeated treatments with ivermectin, the numbers of nematodes in these six hares were compared with those from nine hares that had not been previously trapped or treated, and which served as control hares.

The effect of treatment with ivermectin on numbers of *Protostrongylus boughtoni* and *Nematodirus triangularis*, the two most common nematodes, was determined by a one-way analysis of covariance (ANCOVA) (SYSTAT, Inc., Evanston, Illinois, USA). In Experiment 2, the effects of treatment and time were analyzed by a two-way ANCOVA with treatment and weeks analyzed as fixed effects. Because we had evidence that the size (age) of hares affected nematode numbers (data not shown), the weight of hares at collection was analyzed as a covariate in all three experiments. Nematode numbers were transformed (ln(x + 1)) prior to analysis. The control hares used for the analyses were those animals collected in the same week as treated hares. Mean intensity is defined as the mean number of worms per infected hare in a sample; and prevalence is defined as the proportion of infected hares in the sample (Margolis et al., 1982).

RESULTS

Four species of nematodes were found (Table 1). Infections with *Passalurus* sp. were infrequent in these hares; although this made statistical tests problematical, there was no evidence that ivermectin had any influence on this nematode (Table 1). Prevalences and mean intensities of *Trichuris leporis* were comparable to infections of *Nematodirus triangularis* and *Protostrongylus boughtoni*, but, again, ivermectin had no apparent influence on *T. leporis* (Table 1).

Initial prevalences and mean intensities of *P. boughtoni* and *N. triangularis* varied among experiments. However, both parasites were found in at least one-half of the hares, and, in most experiments, at mean intensities greater than 10 parasites/infected hare. In the ivermectin pen trial, where opportunities for reinfection were very low, *P. boughtoni* was completely eliminated from treated hares, and both prevalences and mean intensities of *N. triangularis* were markedly reduced (Table 1), providing evidence that ivermectin was effective against these two species of nematodes.

In the field trials, where hares had ample opportunities for reinfection, a single dose of ivermectin significantly reduced the numbers of both *P. boughtoni* and *N. triangularis* for up to 4 wk following treatment, but not thereafter (Fig. 1, Table 1) (two-way ANCOVA at 2 and 4 wk with treatment: $F_{1,18} = 9.85$, $P = 0.006$ for *P. boughtoni* and $F_{1,18} = 30.55$, $P = 0.0001$ for *N. triangularis*; and week: $F_{1,18} = 10.93$, $P = 0.004$ for *P. boughtoni* and $F_{1,18} = 16.36$, $P = 0.001$ for *N. triangularis*; and one-way ANCOVA at 7 wk with treatment: $F_{1,14} = 2.10$, $P = 0.17$ for *P. boughtoni* and $F_{1,14} = 0.12$, $P = 0.56$ for *N. triangularis*). Mean intensities in both treated and control hares increased significantly between the second and fourth weeks of Experiment 2. Although there were differences between the means of the treated and control groups at 4 wk there was no significant interaction between treatment and week ($F_{1,18} = 0.27$, $P = 0.61$ for *P. boughtoni* and $F_{1,18} = 0.44$, $P = 0.52$ for *N. trangularis*), providing evidence that after 2 wk the rates of reinfection did not differ between the treated and control groups.

In Experiment 3, where the long-term effects of multiple treatments with ivermectin were assessed, numbers of both species of worms appeared to be reduced in the treated groups at 12 wk post-treatment (Fig. 2, Table 1). However, when body weight was used as a covariate the differences between treated and control groups were not significant (one-way ANCOVA with treatment: $F_{1,12} = 1.77$, $P = 0.14$, for *P. boughtoni* and $F_{1,12} = 1.59$, $P = 0.14$ for *N. triangularis*).

DISCUSSION

A single injection of ivermectin eliminated virtually all adult *Protostrongylus boughtoni* and *Nematodirus triangularis*, and significantly reduced the numbers of these two species of nematode for 4 wk. In itself, the pen trial was inconclusive, in that the lack of untreated penned hares made it impossible to rule out an effect of captivity. However, the close similarity between the results of the pen trial and those of the short-term field experiment supports the interpretation that the drug

TABLE 1. Mean intensity of *Passalurus* sp., *Trichuris leporis*, *Protostrongylus boughtoni*, and *Nematodirus triangularis* infecting snowshoe hares treated with ivermectin, compared to those in untreated hares collected at the beginning of each experiment, and at the end of each experiment when treated hares were collected, July 1990 to November 1991.

Treatment	Experiment 1 Week 7 post treatment (July to August 1990)	Experiment 2 Week 2 post treatment (July to August 1991)	Experiment 2 Week 4 post treatment (July to August 1991)	Experiment 3 Repeated treatments (June 1990 to November 1991)	Pen Trial Week 3 post treatment (August to September 1990)
Passalurus sp.					
Untreated					
Start of experiment	(0/16)[a]	16.0 (1/6)	16.0 (1/6)	—[b]	(0/8)
End of experiment	(0/8)	5.0 (1/6)	2.0 ± 0 (2/7)	228.0 ± 53.7 (2/9)	1.0 (1/10)
Treated	1.0 (1/10)	1.0 (1/5)	1,248.3 ± 2,216.4 (4/5)	16.0 ± 11.3 (2/6)	(0/9)
T. leporis					
Untreated					
Start of experiment	1.0 ± 12.1 (6/16)	30.8 ± 33.8 (4/6)	30.8 ± 33.6 (4/6)	—	10.8 ± 24.4 (4/10)
End of experiment	21.5 ± 30.9 (4/8)	1.5 ± 0.7 (2/5)	1.0 (1/5)	3.7 ± 2.3 (3/9)	15.2 ± 20.8 (8/10)
Treated	37.4 ± 47.2 (8/10)	3.5 ± 1.9 (4/7)	14.2 ± 9.2 (4/6)	4.7 ± 6.4 (3/6)	14.8 ± 9.9 (5/9)
P. boughtoni					
Untreated					
Start of experiment	11.2 ± 7.1 (10/16)	10.4 ± 13.7 (5/6)	10.4 ± 13.7 (5/6)	—	13.8 ± 8.1 (8/8)
End of experiment	13.8 ± 8.1 (8/8)	9.8 ± 6.4 (4/5)	24.0 ± 10.3 (5/5)	17.7 ± 18.9 (7/9)	9.4 ± 5.9 (10/10)
Treated	8.3 ± 6.0 (9/10)	5.5 ± 6.4 (2/7)	16.8 ± 21.2 (5/6)	6.0 ± 6.1 (3/6)	(0/9)
N. triangularis					
Untreated					
Start of experiment	10.0 ± 8.0 (9/16)	37.3 ± 34.5 (6/6)	37.3 ± 34.5 (6/6)	—	5.3 ± 4.6 (4/8)
End of experiment	5.2 ± 4.6 (4/8)	15.0 ± 9.9 (5/5)	60.0 ± 40.4 (5/5)	307.4 ± 486.2 (9/9)	109.0 ± 141.2 (7/10)
Treated	3.7 ± 3.9 (6/10)	3.8 ± 3.8 (6/7)	22.2 ± 22.1 (5/6)	84.4 ± 73.0 (5/6)	1.0 (1/9)

[a] Mean ± SD intensity of infection (number infected/number of hares examined).
[b] —: No hares were examined for numbers of parasites present at the start of experiment 3.

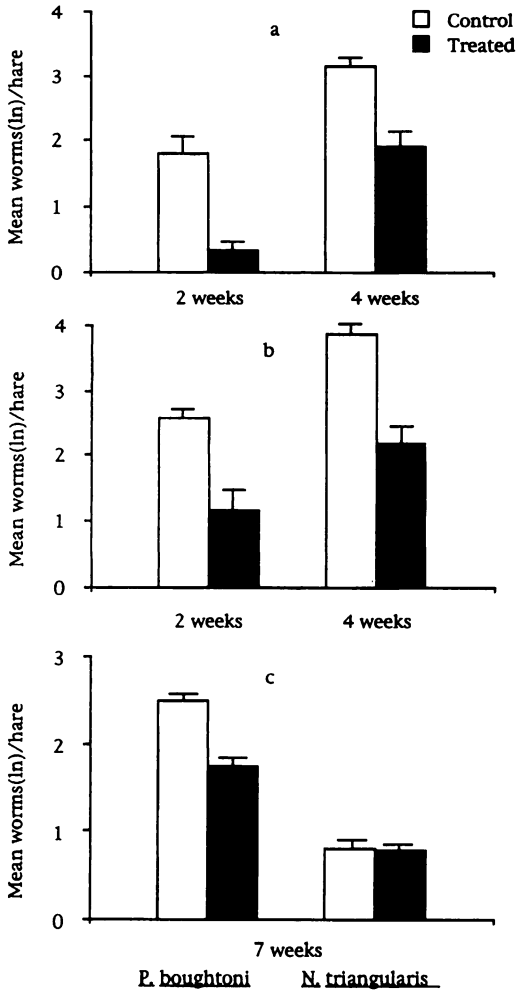

FIGURE 1. Effect of ivermectin on mean (+SE) numbers of *Protostrongylus boughtoni:* (a) and *Nematodirus triangularis*; (b) at 2 and 4 weeks (Experiment 2), and at 7 weeks; (c) (Experiment 1) after a single injection with 0.4 mg ivermectin per kg body weight.

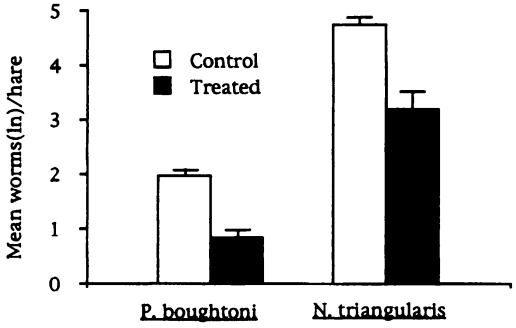

FIGURE 2. Effect of ivermectin on mean (+SE) numbers of *Protostrongylus boughtoni* and and *Nematodirus triangularis* at 12 (±4.7) weeks after multiple subcutaneous injections with 0.4 mg ivermectin per kg body weight.

treatment was responsible for the reduction in numbers of these two nematodes. Thus, injectable ivermectin is potentially useful in manipulative experiments.

However, three results provide evidence that this potential is not as great as anticipated. First, neither single nor multiple injections of ivermectin had any apparent effect on numbers of *Trichurus leporis* or *Passalurus* sp.; however, the low number of cases of the latter may have made it impossible to see any effect of treatment.

Ivermectin has a high therapeutic value against oxyurid worms (Flynn et al., 1989), but its therapeutic effect against trichurids depends upon the host in which the drug is being used (Schillhorn van Veen and Gibson, 1983; Bisset et al., 1990). The inability of ivermectin to affect these parasites in a wild host under natural conditions is evidence of a reduced chemotherapeutic value of ivermectin in a field setting.

Second, almost all treatment groups included one or more treated hares in which numbers of *P. boughtoni* or *N. triangularis* were not reduced. In about half of these cases, numbers of worms of both species were similar to, or higher than, numbers occurring in control hares. There are at least two potential explanations for this lack of efficacy in these hares. First, in sheep dosed subcutaneously with several drugs, there is sometimes a local tissue reaction at the site of injection that restricts the drug to that site (W. L. Shoop, pers. comm.). In such cases the drug is not taken into the blood stream and therefore not delivered to the target parasites. Second, ivermectin itself will paralyze and kill many helminth parasites without assistance from the immune system (Preston, 1984; Casado et al., 1989). However, there are instances in which the immune system in concert with ivermectin plays an important role in the elimination of the worms

(Rao et al., 1987). If the immune system is important in hares, outliers may be immunocompromised individuals. Either or both of these mechanisms could be responsible for the ineffectiveness of the drug treatment in individual hares.

Finally, the reduction in number of worms resulting from treatment with ivermectin was short-lived in free-ranging snowshoe hares. In domestic livestock, laboratory animals, and wild animals kept in captivity after treatment, the worm-reducing effects of ivermectin last for 2 to 3 mo (Alva-Valdes et al., 1988; Baumans et al., 1988; Samuel and Gray, 1988). In free-ranging snowshoe hares, infections with *P. boughtoni* and *N. triangularis* appeared to be reacquired in treated and untreated hares at approximately the same rates after 2 wk. Given the 3 to 4 wk developmental period of *P. boughtoni* (Kralka and Samuel, 1983), it is not likely that the adults of that species found at 4 wk after treatment are derived from new infections acquired after the presumed lapsing of the drug's active period at 2 wk after treatment. Thus, we believe that the drug treatment does not prevent reinfection during its active period, or, more likely, that not all larvae in the tissues were killed by the single treatment. In some hosts, ivermectin is effective against larval worm stages within the tissues (Bisset et al., 1990) and in others it is not (Campbell et al., 1979). In snowshoe hares, we believe that fourth-stage larvae within the lung parenchyma may not be affected by the drug, although they may be prevented from emerging or killed if they do emerge (McGraw and Menzies, 1986). These immature stages may then enter the bronchi and mature when concentrations of the drug in the hare decrease to ineffective levels. A similar pattern may apply to *N. triangularis*. This would account for the decline in efficacy noted in hares collected 4 wk post-treatment. The further decline in efficacy 7 wk after treatment probably is due not only to maturing of larval stages present at the time of treatment, but also to development of parasites that were acquired after the drug had been cleared from the tissues and body fluids of the hare.

The quick recovery in numbers of *P. boughtoni* and *N. triangularis* in treated hares also is evidence of a rapid rate of parasite transmission in this population. Under such circumstances, chemotherapy in free-ranging hares would only be successful if treatments could be repeated every 2 to 4 wk, or if multiple treatments had longer-lasting residual effects. The results of Experiment 3 are evidence that multiple treatments do not have any such longer-lasting residual effect.

Based on our results, we believe that injection of ivermectin is potentially useful in experiments manipulating nematodes in snowshoe hares. Such injections do control the two most abundant and potentially pathogenic parasites in the hare populations we studied (J. S. Sovell and J. C. Holmes, unpubl.). This treatment procedure would seem suitable where a high proportion of the animals can be retrapped and retreated at monthly intervals, where using treated feed is inappropriate, and where analyses are based on data (mortality, natality, condition) on known individuals. The lack of efficacy in some individual hares is evidence that some measure, such as fecal output of eggs or larvae, should be used to segregate out such individuals. The need for frequent retreatments could be minimized by the use of a sustained-release bolus as used for ungulates (Alva-Valdes et al., 1988), or a sustained-release implantable capsule.

In-feed formulations of ivermectin have proven effective in other field settings (Foreyt, 1993). Using treated feed may be preferable where animals are hard to capture at adequate intervals; where data are collected primarily at the population level and where density, mortality or natality are not attributable to individuals; or where there is a rapid turnover in the host population.

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