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Eprinomectin pour-on for control of *Boophilus microplus* (Canestrini) ticks (Acari: Ixodidae) on cattle

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Abstract

The efficacy of a commercial pour-on formulation of eprinomectin, a macrocyclic lactone, against experimental infestations of *Boophilus microplus* (Canestrini) ticks was evaluated in two trials involving 27 *Bos taurus* calves. The first trial was designed to evaluate the effects of a single treatment at a dose of 0.5 mg/kg of body weight against standard size *B. microplus* females (4.5–8.0 mm long). A significant reduction in tick numbers ($P < 0.05$, Wilcoxon test) was observed between treated calves as compared to untreated ones from Day 3 (44% efficacy) after treatment to the end of the trial on Day 28 (96.9%), with a peak efficacy of 97.1% on Day 21. In the second trial the effect of eprinomectin on standard size tick numbers, engorgement weight and fertility of female ticks from calves with a single treatment dose of 1 mg/kg on Day 0 and calves treated twice at a dose of 0.5 mg/kg on Days 0 and 4 was evaluated. An efficacy >93% was obtained from Day 2 to Day 28 after treatment in calves treated twice at 0.5 mg/kg, and to the end of the trial (Day 35) in calves treated once with 1 mg/kg. The 1 mg/kg treatment provided >98% residual efficacy for at least 7 days. During the first part of the second trial the efficacy of eprinomectin resulted from a dramatic adverse effect on engorgement weight and fertility of female ticks, with 100% control on Day 5 (dosage of 1 mg/kg) and on Days 6 and 7 (two doses of 0.5 mg/kg). Following Day 7, most of the effect was due to reduction in the number of standard size female ticks.

Keywords: *Boophilus microplus*; Control; Cattle; Eprinomectin pour-on

1. Introduction

The southern cattle tick *Boophilus microplus* (Canestrini) is detrimental to the cattle industry in tropical and subtropical areas of the world where cattle are commonly treated with sprays or dips for its

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control. Pour-on applications of pesticides are less traumatic to cattle than conventional dippings and several new acaricides are presented in such formulations. Macrocyclic lactones have capacity to simultaneously control several internal and external parasites of cattle. Members of this group, such as ivermectin and moxidectin, applied as pour-on treatment showed efficacy for the control of the southern cattle tick, *B. microplus* (Cramer et al., 1988; Remington et al., 1997; Guglielmone et al., 2000). A novel macrocyclic lactone, eprinomectin, has been registered as a pour-on formulation having the advantage of producing lower residue levels in cattle milk, compared to other formulations of this chemical group.

Recently, Davey and George (2002) showed that eprinomectin pour-on was more effective than ivermectin and moxidectin pour-on applications for *B. microplus* control. They used single and double applications of the dose recommended for the control of internal parasites (0.5 mg/kg), and inferred that even higher tick control could be achieved by using a single dose two to three times higher than the recommended doses. These authors described the general effect of eprinomectin on *B. microplus* ticks and also the impact on female ticks close to completion of their parasitic development. Herein, we present the effects of different treatment regimes with eprinomectin pour-on using calves artificially infested with the southern cattle tick, including a dose twice the recommended for control of gastrointestinal nematodes (1 mg/kg) to confirm if a higher tick control is achieved. The study was also focused to obtain information about detrimental effects of eprinomectin on tick numbers, engorgement weight and fertility of *B. microplus* females obtained at different post-treatment intervals from treated calves, as compared to untreated calves.

2. Materials and methods

The study was carried out in the Estación Experimental Agropecuaria Salta of the Instituto Nacional de Tecnología Agropecuaria (INTA), located in Cerrillos (24°55′S, 65°29′W, altitude 1250 m), Province of Salta, Argentina, using 27 Holstein × Jersey (*Bos taurus*) calves purchased in an adjacent farm before being exposed to *B. microplus* infestation on pastures. The calves were maintained in small paddocks at the INTA and were fed lucerne hay ad libitum before and throughout the study.

The study consisted of two trials. The first was performed with 12 calves infested with 14- to 21-day-old *B. microplus* larvae from the INTA colony. To this end, 5000 larvae were released on each calf on Days 21, 17, 14, 7, 4 and 1 before treatment. Therefore adults, nymphs and larvae of *B. microplus* were on the infested animals the day of treatment (Day 0). On Day 0, calves were divided into two groups of six animals each with one group being designed as a treated group and the other designed as an untreated group. In order to form homogeneously infested groups (Wilcoxon test, $P > 0.50$) with similar mean body weights (*t* test, $P > 0.50$), calves were ranked by tick numbers and weight as described by Guglielmone et al. (2000). The groups were maintained in separate paddocks until the end of the trial. Calves from the treated group were medicated with a commercial pour-on formulation (0.5%) of eprinomectin (IVOMEC® EPRINEX™ POUR ON, Merial Argentina S.A.). The drug was applied to the dorsal midline (from withers to the tail base) at a rate of 1 ml/10 kg of body weight to provide the recommended dose against gastrointestinal nematodes (0.5 mg/kg). Tick burdens were assessed on Days 1, 3, 5, 7, 10, 14, 21 and 28 post-treatment (PT) following the technique of Wharton et al. (1970), based on counts on one side of calves of standard size (SS) *B. microplus* female ticks that were 4.5–8.0 mm long. The percentage efficacy of eprinomectin was measured by using total tick numbers for each group applying the classical formula described by Abbott (1925) when $P < 0.05$ (Wilcoxon test). The objective of this first trial was to confirm that a beneficial effect against a *B. microplus* infestation could be achieved by eprinomectin before proceeding with additional trials.

The second trial involved 15 calves that were infested as in trial one but with an additional infestation of 5000 larvae on each calf on Day 7 PT. Calves were divided into three homogeneous groups of five individuals each according to the level of the SS ticks infestation on Day 0 (Kruskal–Wallis test, $P > 0.50$) and mean body weights (Analysis of Variance, $P > 0.50$). Each group was maintained in separate paddocks. Calves from one group (GT) were treated twice with the commercial pour-on formulation of eprinomectin at a dose of 0.5 mg/kg on Days 0 and 4 PT. Individuals from a second group (GD) were treated once at a dose of 1 mg/kg on Day 0. The remaining group of calves formed the untreated control group. The number of SS female ticks was counted on Days 1, 2, 3, 4, 5, 6, 7, 10, 14, 21, 28 and 35 PT.

On each counting day a maximum of 10 engorged female ticks were forcibly removed from each group of calves (GT, GD and control) if available. The ticks were weighed and maintained in darkness at 27 ± 1 °C, 83–86% of relative humidity to evaluate oviposition, egg-hatching and the Reproductive Efficiency Index (REI) that expresses the number of eggs laid per milligram of body weight (Drummond and Whetstone, 1970). Additionally, a Fertility Efficiency Index (FEI), expressed as the number of hatched larvae per milligram of body weight was obtained. To this end, larvae and unhatched eggs from each egg mass laid by a female tick were counted as described by Guglielmone et al. (1989).

The percentage efficacy of eprinomectin was evaluated on a daily basis as the product of the coefficients of SS tick survival (CTS), engorgement weight (CEW) and FEI (CFEI) in relation to the same parameters for ticks of the control group using the following formula:

$$100\{1 - [(\mathrm{CTS})(\mathrm{CEW})(\mathrm{CFEI})]\}$$

Daily coefficients were obtained when the difference between the corresponding parameters were statistically significant ($P < 0.05$). To this end, Kruskal–Wallis test was applied for SS tick infestation and Analysis of Variance (ANOVA) for REI and FEI. Each coefficient was obtained by using the following formula:

$$\frac{\text{Value for the control group} - \text{Value for the treated group}}{100}$$

where the value for the control group is 100% and the value for the treated group corresponds to the percentage reduction of the corresponding parameter in relation to the treated group.

3. Results

During the first trial the total numbers of SS ticks in the control group ranked between 186 (Day 0) and 750 (Day 21 PT) (Table 1). The effect of a single dose of 0.5 mg/kg of eprinomectin pour-on on SS ticks became evident by Day 5 PT when the reduction in tick number exceeded 50% in relation to the control group. More than 90% reduction of tick numbers was obtained from Day 10 to Day 28 PT, with a maximum of 97.0% on Day 21 (Table 1).

Table 1
Total number of *Boophilus microplus* females 4.5–8.0 mm long counted on one side of calves treated with 0.5 mg of eprinomectin pour-on per kilogram of body weight and controls

Days post-treatment	Total tick numbers		P	Efficacy (%)
	Control group ($n = 6$)	Treated group ($n = 6$)		
0	186	192	>0.50	Not applicable
1	246	220	>0.05	Not applicable
3	252	141	<0.05	44.0
5	241	91	<0.01	62.2
7	405	53	<0.001	86.9
10	443	37	<0.001	91.6
14	654	48	<0.001	92.7
21	750	22	<0.001	97.1
28	514	16	<0.001	96.9

P values (Wilcoxon test) and percentage efficacy obtained with Abbott's formula: ((total ticks control group − total ticks treated group)/total tick control group) × 100.

Fig. 1 illustrates the number of SS ticks counted on GT, GD and control calves throughout the second trial. The biological parameters evaluated on ticks recovered from the GD and GT groups, as well as the percentage reduction in relation to ticks from the control group, are presented in Table 2. The reduction in SS tick number exceeded 50% on Day 4 PT in the GT and GD groups; this reduction was ≥90% from Day 6 to the end of the trial for GD and from Day 10 to 28 for GT.

The adverse effect on engorgement weight of female ticks was evident from Day 1 to the end of the trial in ticks from GD and from Day 1 to Day 14 PT in females from GT. No ticks were recovered from either treated group on Day 28 PT. The engorged ticks recovered from GT on Day 21 and 35 PT were heavier ($P < 0.05$) than those ticks obtained from GD.

The reproduction as measured by REI of ticks from GT obtained on Day 1 PT was not statistically different from the REI of ticks in the control group. However, the corresponding value of the fertility of the ticks as measured by FEI showed that it was already impaired (Table 2). This effect was maintained until Day 14 and

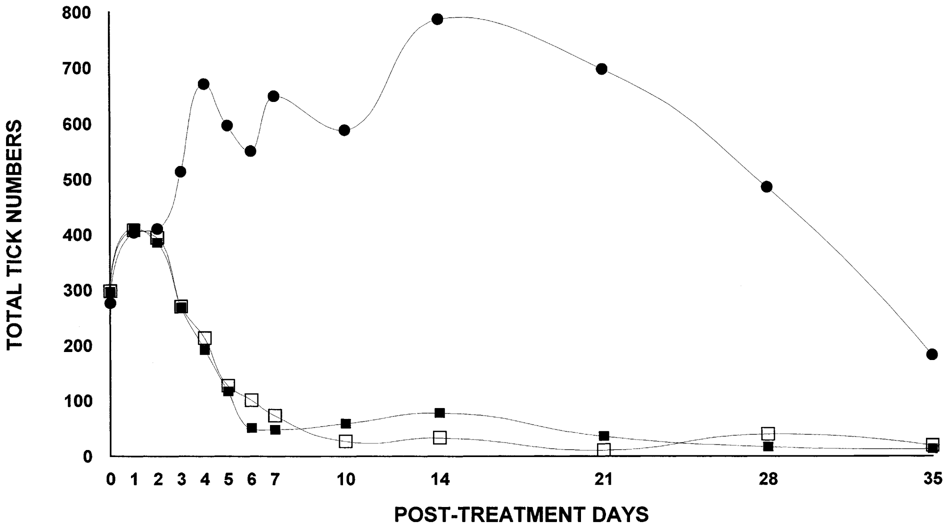

Fig. 1. Total number of *Boophilus microplus* female ticks 4.5–8.0 mm long counted on one side of five calves treated with 0.5 mg/kg of body weight of eprinomectin pour-on on Days 0 and 4 (open squares), five calves treated with 1 mg/kg on Day 0 (filled squares) and five untreated calves (circles).

again on Day 28 PT. Conversely, the REI and FEI of ticks from GD were statistically different from ticks in the control group from Day 1 to the end of the trial.

The percentage efficacy of both eprinomectin treatment regimes are presented in Table 3. They resulted in an efficacy ≥95% from Day 3 after first treatment to Days 28 (GT) or 35 (GD).

The larvae used to infest cattle on Day 7 PT were expected to develop into engorged females from Day 28 to Day 35 based on the fact that most female ticks

Table 2

Total number of *Boophilus microplus* females 4.5–8.0 mm long counted on one side of five calves treated with 0.5 mg of eprinomectin pour-on per kilogram of body weight on Days 0 and 4 post-treatment (GT) and on five calves treated with 1 mg on Day 0 (GD), mean female tick engorgement weight, REI[a] and FEI[b]

Days post-treatment	Total tick numbers		Weight of ticks		REI		FEI	
	GT	GD	GT	GD	GT	GD	GT	GD
0	298	297	227.0	221.0	11.9	11.8	10.9	11.0
1	408	412	126.3 (36.5)	92.2 (53.6)	10.5	8.5 (26.1)	6.0 (47.6)	5.6 (43.9)
2	394	385	55.2 (75.4)	49.0 (78.2)	6.1 (48.7)	5.3 (55.4)	3.1 (72.1)	2.7 (75.7)
3	270 (47.4)	269 (47.6)	50.5 (75.9)	60.1 (75.3)	5.0 (58.0)	6.9 (42.0)	3.7 (65.7)	4.2 (61.1)
4	213 (68.3)	192 (71.4)	42.3 (82.7)	40.5 (83.4)	3.5 (69.6)	3.5 (69.6)	0.6 (94.5)	0.1 (99.1)
5	127 (78.7)	117 (80.4)	23.0 (88.1)	24.0 (87.6)	3.3 (72.7)	0 (100)	1.3 (88.3)	0 (100)
6	101 (81.6)	51 (90.7)	25.0 (88.8)	42.5 (81.0)	0 (100)	6.1 (48.3)	0 (100)	1.3 (88.1)
7	73 (88.8)	48 (92.6)	43.0 (81.7)	43.0 (81.7)	0 (100)	4.5 (61.9)	0 (100)	1.8 (83.8)
10	27 (95.4)	59 (90.0)	36.0 (84.8)	49.7 (79.0)	4.8 (59.0)	7.4 (36.8)	3.4 (67.6)	6.6 (37.1)
14	33 (95.8)	78 (90.1)	72.2 (59.1)	76.4 (56.8)	9.2	8.6 (30.1)	2.8 (72.8)	5.1 (50.5)
21	11 (98.4)	36 (94.8)	206.0	138.4 (42.2)	11.8	10.4 (16.1)	11.2	7.0 (39.1)
28	40 (91.8)	17 (96.5)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)
35	19 (89.6)	13 (92.9)	186.0	124.0 (43.6)	9.8	8.5 (27.3)	7.5	4.9 (54.6)

In parenthesis percentage reduction in relation to the corresponding parameters from control calves if $P < 0.05$ (Kruskal–Wallis test was conducted on ticks number on calves and Analysis of Variance (ANOVA) for other parameters).

[a] Reproductive Efficiency Index (number of eggs/weight of female tick in milligrams).

[b] Fertility Efficiency Index (number of hatched larvae/weight of female tick in milligrams).

Table 3
Coefficients[a] of standard size females (4.5–8.0 mm long) survival (CTS), engorgement weight (CEW), and CFEI[b] in relation to control ticks and percentage efficacy[c] against *Boophilus microplus* infestations on calves treated with 0.5 mg of eprinomectin pour-on per kilogram of body weight on Days 0 and 4 post-treatment (GT) and on calves treated with 1 mg on Day 0 (GD)

Days post-treatment	GT				GD			
	CTS	CEW	CFEI	Efficacy (%)	CTS	CEW	CFEI	Efficacy (%)
0	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]
1	–[d]	0.635	0.524	66.7	–[d]	0.464	0.561	74.0
2	–[d]	0.246	0.279	93.1	–[d]	0.218	0.243	94.7
3	0.526	0.241	0.343	95.7	0.524	0.247	0.389	95.0
4	0.317	0.173	0.055	99.7	0.286	0.166	0.009	99.9
5	0.213	0.119	0.117	99.7	0.196	0.124	0.000	100
6	0.184	0.112	0.000	100	0.093	0.190	0.119	99.8
7	0.112	0.183	0.000	100	0.074	0.183	0.162	99.8
10	0.046	0.152	0.324	99.8	0.100	0.210	0.629	98.7
14	0.042	0.409	0.272	99.5	0.099	0.432	0.495	97.9
21	0.016	–[d]	–[d]	98.4	0.052	0.578	0.599	98.2
28	0.082	0.000	0.000	100	0.035	0.000	0.000	100
35	0.104	–[d]	–[d]	89.6	0.071	0.564	0.454	98.2

[a] Each coefficient was obtained as the difference between 100% (any parameter for control group) and percentage reduction in treated groups/100. Coefficients were calculated only if differences between control and treated groups were statistically significant ($P < 0.05$) using Kruskal–Wallis test for standard female tick infestations and Analysis of Variance (ANOVA) for other biological parameters.
[b] Fertility Efficiency Index (number of hatched larvae/weight of female tick in milligrams).
[c] Percentage efficacy obtained with the formula: $100\{1 - [(CTS)(CEW)(CFEI)]\}$.
[d] No significant differences with ticks from the untreated control group.

complete their parasitic life cycle before 29 days (Hitchcock, 1955; Nuñez et al., 1972). On Day 35 PT the efficacy was of 89.6% and 98.2% for GT and GD, respectively, showing a higher residual effect in the latter group.

The engorgement weight of females obtained from GT and GD from Day 3 to Day 14 PT was extremely low (Table 2). Nevertheless, some of these females were able to lay fertile eggs and produce viable larvae, for example, one engorged female weighing 29 mg laid 234 eggs that produced 114 larvae.

While the overall effect of eprinomectin (all treatment regimes) on tick control could be judged as adequate, some variation was observed among individual calves. Almost all engorged female ticks from GD obtained from Day 7 to Day 21 PT were collected from the same calf.

4. Discussion

This study confirms the value of pour-on eprinomectin in the control of *B. microplus* infestations on cattle. Its use on lactating dairy cows would be especially advantageous because milk residues of the drug in cows treated with one dose of 0.5 mg/kg are low enough to guarantee that the product has no risk for human consumption (Alvinerie et al., 1999).

The study was conducted on the assumption that if a single dose of 0.5 mg/kg of eprinomectin substantially reduced the number of SS females on cattle, then a double dose at 0.5 mg/kg or a single dose at 1 mg/kg might provide even higher control. However, no obvious effect related to dose rate was found on the survival of SS female tick numbers in this study.

A greater adverse impact on weight and fertility of female ticks recovered from calves treated with a single dose of 1 mg/kg of eprinomectin was observed than from ticks recovered from calves treated with two doses of 0.5 mg/kg with a 4-day interval. However, the overall percentage efficacy was quite similar for both treated groups from Day 1 to Day 28 PT. The efficacy of eprinomectin resulted mostly from the impairment of engorgement weight and fertility of treated female ticks from Day 1 to Days 5 and 7 PT for GD and GT, respectively. This effect of eprinomectin on *B. microplus* females near to detachment from calves was previously described by Davey and George

(2002). Beyond Days 5–7 PT the efficacy of both treatments was a result of the mortality of larvae, nymphs and young adult ticks as reflected by the low numbers of SS female ticks registered on GD and GT after Days 6 and 10 PT, respectively. This was the most persistent effect of eprinomectin, yielding similar values ($P > 0.05$) for GD and GT until Day 28 PT, as showed in Fig. 1. The few ticks able to engorge during this period were capable of laying an increased proportion of viable eggs, except at Day 28 PT, when no engorged females detected from any treated calf.

Most of the engorged females that detached from calves of both treated groups between Day 2 and Day 14 PT were small in size. Nevertheless, some of them were able to lay fertile eggs. Bennett (1974) reported that the optimal weight for *B. microplus* engorged females was 160–300 mg. That author also stated that all females with a minimum weight of 20 mg laid eggs. It is possible that smaller ticks detaching from cattle treated with eprinomectin are less viable under field conditions than untreated ticks and the same may be true of the larvae derived from them. It would be of interest to study these facts to better determine the actual efficacy of eprinomectin and other macrocyclic lactones against *B. microplus* ticks.

Alvinerie et al. (1999) showed that the peak concentration of eprinomectin in plasma of cattle treated with 0.5 mg/kg occurred on Day 2 PT. Endectocide drugs acts slowly on ectoparasites, which could be explained by the progressive paralysis of the parasite's feeding mechanism (Jackson, 1989). It is likely that the earlier achievement of 100% efficacy in calves treated once with 1 mg/kg (Day 5 PT) compared to calves treated twice with 0.5 mg/kg (Days 6 and 7 PT) could be explained by an initially higher eprinomectin blood concentration in the former group. The highest efficacy obtained on GT occurred shortly after the second administration of eprinomectin, and was likely a consequence of the enhanced plasma concentration of the drug. Surprisingly, calves from GD showed a higher efficacy of 97% on Day 35 PT, while calves from GT showed an efficacy lower than 90% on the same day. Additional information on the kinetics of eprinomectin in cattle under different dosage regimes is needed to further understand the effect of this drug on *B. microplus* ticks.

Knowledge regarding individual cattle variation of eprinomectin pharmacokinetics will also be important in explaining why almost all ticks recovered from GD were obtained from just one calf. Such variation has also been observed in other macrocyclic lactones, such as moxidectin and ivermectin, administered as a pour-on to cattle (Gayrard et al., 1999; Laffont et al., 2001; Sallovitz et al., 2002). Licking accounts for mechanical transfer among cattle treated with macrocyclic lactones applied as a pour-on (Laffont et al., 2001; Barber and Alvinerie, 2003). It could be possible that differential licking may result in higher or lower doses in some individuals originally treated with the same concentration of eprinomectin. Nevertheless, individual animal variation in the kinetics of eprinomectin may also be a plausible explanation for different effects of this drug on ticks from calves of the same treatment group. Alvinerie et al. (1999) showed that plasma and milk concentration of eprinomectin vary widely among milking cows following pour-on treatment. Moreover, large individual variation in the concentration of moxidectin deposition has been found in tissues of sheep treated with an injectable formulation (Lifschitz et al., 2000). As reported by Lanusse (2003), bioavailability of macrocyclic lactones is a complex process influenced by cattle breed, feed intake, nutritional status, and body composition. It is possible that a combination of these factors results in a lower availability of eprinomectin in some individuals. This is an important aspect that merits further investigation especially in measuring failure risks in a hypothetical scenario of using eprinomectin in a *B. microplus* eradication campaign.

Even a single dose of 0.5 mg/kg eprinomectin used for treatment against gastrointestinal nematodes of cattle provided adequate efficacy in controlling infestations of *B. microplus* ticks, as shown by the >90% reduction of SS tick numbers from Day 10 (91.6%) to Day 28 (96.9%) PT. The residual efficacy of >98% lasted at least 1 week in calves treated with 1 mg/kg of eprinomectin and improved the results of two treatments of 0.5 mg/kg with an interval of 4 days. Nevertheless, additional trials under field conditions are still needed to further confirm the benefits of eprinomectin as an additional tool for the control of *B. microplus* ticks, especially on lactating dairy cows. Pharmacokinetic evaluations in cows subjected to such eprinomectin dosage regimes will also be needed to assure that milk residue levels are below the required concentration for human consumption

(≤30 ng/ml) (Alvinerie et al., 1999). This objective appears feasible in cattle because the peak of eprinomectin concentration in milk after treatment with 0.5 mg/kg was only 4 ng/ml (Alvinerie et al., 1999).

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