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Research paper

Efficacy of a topical combination of fipronil-permethrin against *Rhodnius prolixus* on dogs

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ABSTRACT

A controlled clinical trial was carried out to assess the mortality and repellency of a new topical combination of fipronil-permethrin (Effitix® Virbac, Mexico) against *Rhodnius prolixus* in dogs. Ten medium-size dogs (10 − 15 kg) with short hair were used. The dogs were exposed to 8 adult triatomines once weekly for 7 weeks. On the control day (D0), the dogs were exposed to the insects without treatment. On D7, the dogs were immediately treated with a spot-on 2.2 ml pipette containing 134 mg of fipronil and 1200 mg permethrin after exposure to the insects. The dose was repeated after 4 weeks following the manufacturer's instructions. Repellency at D0 was, 0 % and the insects had a high blood content. After 12 h post-contact, repellency was 86.3 % and slowly decrease though D21 and D28. On D7, none of the insects survived after 3 h of feeding on the treated dogs. On D14, D35 and D42, all insects died within 12 h post-feeding, whereas no mortality was observed in the control D0 ($P < 0.05$). The results of this study indicated that administration of the product following the manufacturer's instructions was efficacious at inducing rapid mortality of *R. prolixus* and therefore could be useful to prevent the transmission of American trypanosomiasis in dogs.

1. Introduction

American trypanosomiasis (AT) is caused by the flagellate protozoan *Trypanosoma cruzi* (*T. cruzi*) and is transmitted to mammals mainly by vectors of the family *Reduviidae.* (Gürtler et al., 2009a; World Health Organization, 2018). Therefore, in regions where AT is endemic, strategies to reduce its incidence have focused on controlling the vectors through sanitary methods, community education and fumigation with various insecticides. Organophosphates, carbamates, pyrethrins and synthetic pyrethroids have been frequently been used (de Fuentes-Vicente et al., 2018). However, fumigation control strategies have faced several problems, primarily high operating costs, suboptimal residual effects and toxicity to humans; in addition, the excessive use of pesticides in some areas has created resistance or failed to interrupt the domestic and peridomestic cycles of *T. cruzi* (Schofield et al., 1987). Domestic dogs, cats, opossums and rodents play important roles in the ecology and epidemiology of AT (Gürtler et al., 2009a). Dogs are the main domestic reservoir of *T. cruzi*, and the presence of animals seroreactive to *T. cruzi* in the household increases the risk of human infection (Gürtler et al., 1993; Jiménez-Coello et al., 2010). In addition, domestic animals provide a link between the peridomestic and forest cycles of *T. cruzi* (Gürtler et al., 1993; Arce-Fonseca et al., 2017). Eliminating infected domestic animals is not a feasible alternative, and therefore, the prevention and control of vector activity are needed to reduce the risk of human infection (Gürtler et al., 2009b).

Due to their important role in the maintenance of *T.cruzi* and its transmission to humans, dogs should be considered a complementary target of AT control (Travi, 2019).Various prevention and control strategies involving the application of insecticides against reduvids through different routes have been explored. These approaches include collars impregnated with deltamethrin (Reithinger et al., 2005), xenointoxications with organochlorines (Schofield, 2000), and treatment of birds, dogs and goats with fipronil as a spray (Gentile et al., 2004) or as spot-on application (Gürtler et al., 2009b). More recently, the use of systemic insecticides on dogs such as isoxazolines and spinosad has been evaluated (Loza et al., 2017; Laiño et al., 2019).These products all have limited or transitory effects on the feeding and mortality of different triatomine species, and consequently their use could be suboptimal for preventing or controlling *T. cruzi* transmission to humans and domestic animals.

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The combination of fipronil and permethrin has repellent and insecticidal effects on *Ctenocephalides felis* (Chatzis et al., 2017; Fankhauser et al., 2015a), *Dermacentor reticulatus*, *Rhipicephalus sanguineus* (Cvejié et al., 2017), *Ixodes ricinus* (Endris et al., 2002), *Culex pipiens* (Franc et al., 2015a), *Aedes albopictus*, *Aedes aegypti* (Fankhauser et al., 2015b) and *Phlebotomus perniciosus* (Franc et al., 2015b). Cardoso (2015) described the combined use of fipronil-permethrin in domestic animals as an effective strategy for reducing the risk of transmission of zoonotic pathogens and Navarro et al. (2016) showed that this combination is a useful and highly effective strategy for the control of infestations by disease-transmitting vectors. Therefore, this combination may have potential as a vector control strategy in dogs, but there are no studies of the use of the fipronil-permethrin combination for the control of reduvids. Consequently, the objective of this study was to evaluate the repellent and insecticidal efficacy of fipronil-permethrin in spot-on mode against the Reduviidae family member *Rhodnius prolixus* in dogs.

2. Materials and methods

2.1. Place of study

The study was performed at the Faculty of Veterinary Medicine of the Autonomous University of Yucatan (UADY) in Southern Mexico, where AT is endemic.

2.2. Animals and study model

The study was approved by the bioethics committee of the Campus of Biology and Agricultural Sciences (CB-CCBA-M-2019-002) of UADY.

For this study, 10 rescued mixed-breed dogs (6 females and 4 males), between 1 and 4 years of age and of medium size (10 − 15 kg) with short hair were used. Two weeks before the application of the product, all animals underwent a clinical examination to verify their health status and were dewormed and vaccinated against rabies. To verify that all animals were free of *T. cruzi* antibodies, an enzyme-linked immunosorbent assay (ELISA) was performed on each animal and later confirmed by Western blot test according to the methodology used by Jiménez-Coello et al. (2010). Throughout the study, the dogs were observed daily to monitor their general health condition.

As a study model, adult female nymphs of *R. prolixus* that were free of *T. cruzi* were used. Reduvids were grown in the Cell Biology Laboratory of the Dr. Hideyo Noguchi Research Center-UADY and starved for 3 weeks before application to the dogs.

2.3. Treatment

An experimental study with a duration of 7 weeks for each dog was conducted. On Day 0 (D0) corresponded to the control day, and Day 7 (D7) through Day 42 (D42) corresponded to weekly time points post-fipronil-permethrin treatment.

Spot-on was the mode of treatment administration. The animal's fur was separated at the midline until the skin was visible. Three different points were taken as a reference: between the shoulder blades and the second and third parts of the body. The product was delivered by placing the tip of the pipette directly against the skin and pressing the applicator in a cranial-caudal direction until its contents were completely emptied. The dose was designed for dogs with a mass of 10 − 15 kg, and each milliliter contained 61 mg of fipronil and 545 mg of permethrin. Thus, the dogs received 134 mg/kg of fipronil and 1200 mg/kg permethrin delivered through the 2.2 ml pipette.

2.4. Exposure to *R. prolixus*

Once weekly during the 7-week study period, each dog was exposed to 8 different virgin females of *R. prolixus* that were weighed before exposure. On the control day (D0), the dogs were exposed to 8 adults of *R. prolixus* without the previous application of fipronil-permethrin, and the results were recorded. The fipronil-permethrin product was first applied on D7, 24 h before exposure to virgin female bugs. On day 35, a re-dosing was applied as suggested by the manufacturer. Each dog was observed for 4 h after treatment to evaluate any adverse reaction to the product.

For each dog, the 8 insects were divided into 2 groups of 4 insects each. Each insect was weighed and individually placed in a 50-ml centrifuge tube (Falcon brand) to prevent contact between the insects during the feeding. Dogs in the standing position were exposed simultaneously to the two groups of tubes by opening the containers vertically in contact with the dog in two areas: over the chest and over the abdomen. The tubes were left in place for 25 min, and movement of the dogs was avoided. A room with coated light inlets was used for the maintenance and control of darkness, temperature and humidity. After 25 min, the tubes were removed, and the two areas of the dog were cleaned to determine if the insects had defecated. Since vectorial transmission of *T. cruzi* occurs through insect dejections after feeding, the record of the number of insects that defecate was relevant.

To evaluate repellency, the amount of blood intake was established by assessing the silhouette of the promesenteron as indicated by Montenegro (1983); briefly, feeding outcome was classified as type 1 (fasted adults; empty promesenteron with the presence of some bubbles), type 2 (adults with little reserve; a narrow strip of dark color and variable shape that does not occupy more than 30 % of the observation area), type 3 (adults with good food reserve; 40–100% of the area observed is dark) and type 4 (adults with a high blood content; ingurgitated). After exposure, the individual insects were re-weighed, placed on filter paper and classified as live or dead. The insect was considered dead if no locomotor activity was observed either spontaneously or upon stimulation with a clamp. Live insects were monitored for periods of 3, 8, 12, 24 and 48 h to assess their blood meal status and their mortality.

2.5. Statistical analysis

For mortality, survival analysis was performed using the Kaplan-Meier method together with a log-rank hypothesis test to determine if the curves were different between weeks of treatment. For the repellency, a chi-square test was performed comparing the days of treatment (D7 to D42), and to correct for the level of error, the Bonferroni test was performed (a method used to counteract the problem of multiple comparisons). Differences were considered significant at $P < 0.05$. All the data were analyzed with the program R (version 3.6.0).

3. Results

3.1. Repellency

As expected, before insecticide application on D0, all insects were ingurgitated showing a high blood content (type 4) indicating no repellent effect. All insects defecated after feeding. In the weeks following the first insecticide treatment (D14, D21 and D28), the repellent effect ranged between 50 and 75 %. Some insects had a good food reserve (type 3–4) (Table 2), but all died within a period of 12 h after exposure (Table 1). On D28, four of the nine insects with type 4 of blood content defecated after feeding; whereas on D42, none of the two animals with type 4 blood content defecated.

3.2. Mortality

On D7, none of the insects survived 3 h after exposure; on D14, D21 and D28, some insects were still alive after 3 h after exposure, but all died within a period of 12 h (Table 1). On the remaining days (D35 and D42), most of the insects died within a period of 3 h; only one insect

Table 1
Survival and mortality of insects after exposure to fipronil-permethrin during the 7 weeks of the study.

Days	Survival % (n)						Cumulative mortality (%)
	3 h	CI 95%	12 h	CI 95%	24 h	48 h	
0	100 (0)[a]	–	100 (0)	–	100 (0)	100 (0)	0
7*	0 (80)[b]	–	–	–	–	–	100
14	8.8 (73)[b]	0.04 – 0.17	91.2 (7)	–	–	–	100
21	48.7 (41)[b]	0.38 – 0.61	11.3 (30)	0.06 – 0.20	0(9)	–	100
28	82.5 (14)[b]	0.74 – 0.91	35.0 (38)	0.26 – 0.47	0(28)	–	100
35*	1.3 (79)[b]	0.00 – 0.08	0 (1)	–	–	–	100
42	10 (72)[b]	0.05 – 0.19	0 (8)	–	–	–	100

CI = confidence interval.
[a] Different letters between days after treatment (3 h columns) represents a statistically significant difference (P = < 0.05).
* Application of fipronil-permethrin.

Table 2
Classification of insects after exposure to fipronil-permethrin with respect to the promesenteron silhouette (Montenegro, 1983) and repellent effect.

Day	Classification n = 80(%)		Repellency n = 80 (%)
	type 3	type 4	
0	0	80 (100)	0 (0)
7*	10 (12.5)	1 (1.3)	69 (86.3)[a]
14	18 (22.5)	0	62 (77.5)[ab]
21	16 (20)	5 (6.3)	59 (73.8)[ac]
28	21(26.3)	9 (11.3)	50 (62.5)[ad]
35*	5 (6.3)	0	75 (93.8)[abcd]
42	13 (16.3)	2 (2.5)	65 (81.3)[a]

[abcd] Different letters between days of treatment (Repellency column) indicate a significant difference (P = ≤0.05).
* Application of fipronil-permethrin.

survived 12 h on D35 but eventually died.

4. Discussion

This study evaluated the efficacy of fipronil-permethrin applied to dogs as a killing or repellent agent for reduvids attempting to feed.

The repellent effect of the product was evaluated by observing the blood intake of the triatomines upon exposure to the dogs. The repellency results obtained in our study are similar to those reported by Endris et al. (2002) for *Ixodes ricinus*. Repellency is important both from an epidemiological standpoint, by preventing the domestic transmission of *T. cruzi* by infected triatomines, and also from a clinical perspective, bypreventing potential allergic reactions, inflammation and pain caused by reduviid saliva.

The repellent effect of the combination is due to permethrin. Throughout the course of the present study, 50–75% of the triatomines remained unfed. Permethrin also contributes to insect paralysis and overturning as previously described (Alzogaray and Zerba, 2017). Permethrin exhibit a 63.4%–80.2% repellent effect against *Ixodes ricinus* with a duration of 5 weeks (Endris et al., 2002). Permethrin affects the CNS of triatomines via constant depolarization and opening of sodium channels for prolonged periods, resulting in permanent depolarization of the axonal membrane and paralysis of the insect (Alzogaray and Zerba, 2017; Soderlund and Knipple, 2003; Katz et al., 2008). The combined action of fipronil- permethrin provides greater insecticidal potency (Cardoso, 2015), even if the contact time between the triatomine and skin of the host is short (Palomino et al., 2008).

The insecticidal effect of the product was observed starting on D7, with 0 % insect survival at 3 h after contact. The survival period increased over the time after product application, but triatomine death occurred in a period no longer than 24 h after contact. A gradual decrease in killing speed as a function of time post-application was previously reported for several hematophagous arthropods, such as *C. pipiens* (Franc et al., 2015a), *C. felis* (Chatzis et al., 2017), *R. sanguineus* (Cvejié et al., 2017) and *P. perniciosus* (Franc et al., 2015b). These studies observed 100 % mortality within 24 h, and this period gradually decreased until day 28 after application. The main metabolites of the formulation (fipronil, fipronil-sulfone and permethrin) accumulate in the hair layer and sebaceous cells soon after administration. These metabolites subsequently decrease over time but can still be detected up to 35 days after application (Beugnet and Franc, 2012). In the present study, a second dose was applied on D35 following the manufacturer's instructions, resulting in high mortality in less than 12 h and confirming the efficacy observed in the previous weeks.

The effects of the fipronil-permethrin combination are due to the pharmacological properties of each component. The insecticidal effect is attributed to the fipronil molecule, which has little effect on triatomine feeding activity (Gürtler et al., 2009a) but alters the function of the CNS cells. Fipronil interrupts the passage of chloride ions through the chlorine channels regulated by GABA, leading to paralysis and immediate death (Zhao et al., 2004; Gupta and Milatovic, 2014). A single dose of fipronil (10 mg/kg pour-on) was previously shown to be efficacious against *Triatoma infestans* with 88.8 % mortality at 72 h even after 30 days after administration (Gentile et al., 2004). In the present study, a higher dose of fipronil (13.4 times higher) was used, and thus insect mortality occurred more rapidly, with a prolonged duration of efficacy but without causing overdose in dogs.

Regarding triatomine control for dogs, the formula evaluated in this study exhibited better insecticide and repellent efficacycompared with other commercial products. For example, Loza et al. (2017) compared three orally administered systemic insecticides (fluralaner, afoxolaner and spinosad) with delayed insecticidal effects. Death of triatomines occurred 120 h after feeding on fluralaner-or afoxolaner-treated dogs. By contrast, no lethal effects of triatomine exposure to spinosad were observed up to 5 days after contact. Deltamethrin, an analogue of permethrin, produced 71 % mortality 27 days after utilization on dog collars. There was no impairment of feeding on dogs, but the fertility of the insects was reduced (Reithinger et al., 2005). Therefore, the performance of available insecticide products for reduvids is suboptimal compared with the combination of fipronil-permethrin reported in this study. This product has the potential of become a useful tool to curb *T. cruzi* transmission to dogs and contribute to Chagas disease control as previously suggested (Travi, 2019).

5. Conclusion

The use of fipronil-permethrin on dogs is highly effective for repelling and killing *R. prolixus* within the time frame recommended by the manufacturer. These results will support the implementation of large field studies to confirm the applicability of this combination for the domestic control of Chagas disease vectors.

CRediT authorship contribution statement

A. Ucan-Mézquita: Data curation, Formal analysis, Investigation. **M. Jimenez-Coello:** Conceptualization, Investigation, Project administration. **E. Guzmán-Marín:** Formal analysis, Investigation, Supervision. **E. Gutierrez-Blanco:** Supervision, Validation, Writing - original draft. **J.I. Chan-Pérez:** Investigation, Resources, Supervision, Validation. **B.L. Travi:** Conceptualization, Writing - original draft. **I. Hernandez-Cortazar:** Investigation, Methodology. **A. Ortega-Pacheco:** Conceptualization, Funding acquisition, Supervision, Writing - original draft.

Declaration of Competing Interest

The authors of this manuscript do not have financial or personal relationships with other persons or organizations that may inappropriately influence or bias the content of this document.

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