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Assessment of the anti-feeding and insecticidal effects of the combination of dinotefuran, permethrin and pyriproxyfen (Vectra® 3D) against Triatoma infestans on rats

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Abstract. This study, based on the rat model, was designed to explore the anti-feeding and insecticidal efficacy of a topical ectoparasiticide, dinotefuran–permethrin–pyriproxyfen (DPP), against Triatoma infestans (Hemiptera: Reduviidae), a vector of Trypanosoma cruzi (Trypanosomatida: Trypanosomatidae), for which dogs are domestic reservoir hosts. Twenty rats were divided into two equal groups: untreated and treated. Each rat was exposed under sedation to 16 T. infestans of mixed life stages for 1 h on days 1, 7, 14, 21 and 28 post-treatment. The anti-feeding and insecticidal effects of DPP were estimated after 1 h of exposure. Insecticidal efficacy was also assessed after incubation of the insects for 24 h post-exposure. Anti-feeding efficacy was 96.7, 84.7, 80.5, 81.5 and 42.6% on days 1, 7, 14, 21 and 28, respectively. Insecticidal efficacy evaluated at 1 and 24 h after exposure on days 1, 7, 14, 21 and 28 was 100, 91.2, 82.5, 80.0 and 29.1, and 100, 100, 100, 96.0 and 49.9%, respectively. This study demonstrates that a single administration of DPP spot-on treatment at a dose equivalent to the minimal recommended dose in rats has a powerful effect against T. infestans starting from day 1 that lasts for at least 3 weeks.

Key words. Triatoma infestans, Trypanosoma cruzi, ectoparasiticide, efficacy, rat model.

Introduction

Chagas’ disease, also known as American trypanosomiasis, is a tropical parasitic disease caused by the protozoan Trypanosoma cruzi. An estimated 6 million people infected with T. cruzi currently reside in the endemic regions of Latin America [World Health Organization (WHO), 2015]. The protozoan parasite T. cruzi is mainly transmitted through the faeces or urine of infected blood-sucking insects of the family Reduviidae, subfamily Triatominae (WHO, 2016). Triatomine bugs, especially Triatoma infestans and Rhodnius prolixus (Hemiptera: Reduviidae), are considered to be the most relevant vectors of T. cruzi because of their anthropophily, high density in peridomicestic areas, good adaptation to human dwellings and T. cruzi vectorial capacity (Noireau et al., 2009), as well as for their wide geographic distribution, principally in Latin America (Noireau, 2009). It is important to stress that the vector elimination programme started in 1991 that aimed to eradicate Chagas’ disease in Southern Cone countries such as Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay produced good results in terms of the elimination of T. infestans in some South American countries. For example, the greatest successes were obtained
by Uruguay in 1997, Chile in 1999 and Brazil in 2006, all of which were certified by the Pan American Health Organization (PAHO)/WHO as free from *T. infestans* (Dias, 2009; Abad-Franch *et al.*, 2013). However, it is important that these countries remain vigilant if they are to avoid the reintroduction of *T. infestans*, which still exists in Argentina, Bolivia, Paraguay and Peru, and of other species that have not been eliminated (Abad-Franch *et al.*, 2013).

*T. infestans* prefers to feed on humans and domestic animals in homes. It derives its bloodmeals from four main sources: humans, chickens, dogs and cats (Gürtler *et al.*, 2014; Provecho *et al.*, 2014; Coura, 2015; Cecere *et al.*, 2016). *T. infestans* nests in thatched or straw roofs, in the crevices of mud walls, and in cement and brick. Other than vector control with insecticides, there is no way to control Chagas’ disease, no vaccine and no effective treatment for chronic forms (WHO, 2006). Because triatomines can live in homes, prevention includes cleaning, the use of mosquito nets and insecticidal treatment of the premises. This prophylaxis gives results, but resistance to mono-insecticides has been detected (Gomez *et al.*, 2014; Mougabure-Cueto & Picollo, 2015) and some insecticides most commonly used for the chemical control of insects are not effective against triatomin bugs (Gürtler & Cardinal, 2015). The role of the dog in the parasitic cycle is now better understood as a result of molecular biology studies (Charles River Laboratories, Saint-Germain-Nuelles, France), with a mean ± standard deviation (SD) weight of 160.7 ± 3.6 g, housed in groups of two individuals per cage (58 × 36 × 20 cm³) at a temperature of 22 °C under an LD 12:12 h cycle. Rats were fed an appropriate maintenance ration of commercial food pellets. Water was available *ad libitum*. The rats were handled according to French rules on the protection of animals used for scientific purposes (decree no. 2013-118; 1 February 2013, Paris) (Legifrance, 2015). The protocol for this study was reviewed and approved by the Ethics Committee for Animal Experimentation at Aix-Marseille University (approval no. 2015/09/01/10122337). General health observations were performed at least twice per day from the start of the acclimation period to the end of the study.

### Source of *T. infestans*

Adult *T. infestans* (CEPEIN susceptible strain) were taken from a laboratory colony initiated in 2009 using adult specimens sourced from Argentina. Since then, this colony has been reared at the laboratory without exposure to any insecticides. All bugs were reared in the laboratory’s insectarium at 26 ± 1 °C and 70 ± 1% relative humidity (RH). The bugs were fed with defibrinated human blood (under an agreement with the Etablissement Français du Sang) using a Hemotek membrane feeding system (Discovery Workshops, Accrington, U.K.). Nymph instars and adults of both sexes were used in the present study. Each rat was exposed to a total of 16 triatome bugs, including 12 nymph instars (three specimens of each of stages 2, 3, 4 and 5) and four adult triatomines. All bugs were starved for 15 days before they were given access to the rats.

### Treatment

The minimum recommended dose in dogs [i.e. 6.4 mg/kg body weight (BW)] of dinotefuran, 0.6 mg/kg BW of pyriproxyfen
and 46.6 mg/kg BW of permethrin] was used to determine the
dose to be administered to rats with a mean ± SD weight of
160.7 ± 3.6 g. As the dose per kilogram BW for one species
cannot be transposed to another species, it was decided that
doses expressed in mg/kg BW for dogs should be converted
equivalent doses based on body surface area in rats and
expressed as mg/m² as previously described by Freireich et al.
(1966). The minimal recommended dose of DPP was therefore
estimated to be 0.07 mL per rat. All doses were administered on
day 0 and were applied directly to the skin as a line-on treatment
along the spine using a micropipette to ensure accurate and
complete dosing. Treated rats were observed several times per
day for 15 min after treatment for general health status and any
adverse events that might be associated with the administration
of the agent.

**Exposure of rats to T. infestans**

Before exposure, all rats were anaesthetized with an intraperi-
toneal injection of a combination of 90 mg/kg ketamine
(Imalgene® 500; Merial, Lyon, France) and 10 mg/kg xylazine
(Rompun® 2%; Bayer Santé Animale, Lyon, France). Each rat
was placed in a transparent plastic container (50 × 20 × 20 cm³)
in which it was then exposed for 1 h to starved nymph instars
(n = 12) and male and female adults (n = 4) on days 1, 7, 14, 21
and 28 post-treatment. The whole experiment was conducted
in a slightly darkened room at a mean ± SD temperature of
22 ± 1°C. After the 1-h exposure period, the bugs were catego-
rized and counted as fed or unfed and dead or live. Live bugs
from each group were maintained in separate incubators and
survival rates at 24 h after the end of the exposure were recorded
(Fig. 1).

**Statistical analysis**

In the present study, each rat represented the experimental
unit. The primary endpoints were the fed and live bug counts.
The arithmetic mean numbers of engorged bugs and live bugs
were calculated at each time-point. Anti-feeding and insecticidal
efficacies were calculated using Abbott's formula (Abbott,
1987) as:

\[
\text{Anti-feeding efficacy (\%) = 100 \times \frac{MCe - MTe}{MCe}}
\]

where MCe represents the mean [geometric mean (GM) or
arithmetic mean (AM)] number of fed bugs in the control
(untreated) group, and MTε represents the mean (GM or AM)
number of fed bugs in the treated group and:

\[
\text{Insecticidal efficacy (\%) = 100 \times \frac{MCi - MTi}{MCi}}
\]

where MCi represents the mean (GM or AM) number of live
bugs in the control (untreated) group, and MTi represents the
mean (GM or AM) number of live bugs in the treated group.

Statistical analyses were performed using STATISTICA Version
each time-point, differences between treated and untreated rats
were compared using Student’s t-test. Statistical significance
was declared at a two-sided P-value of 0.05.

**Results**

No adverse effects of treatment were observed in any of the
treated rats. The proportions of fed bugs in the untreated groups
ranged from 94.3 to 99.5%, with an average of 97.2 ± 1.9%,
throughout the study (Table 1). In both groups, T. infestans
bugs introduced into the plastic containers holding the rats
immediately attacked the rats. Bugs showed conspicuous signs
of feeding after 10–20 min of exposure to untreated control rats.
Generally, adult bugs fed longer than instar nymphs. It was noted
that the bugs always defecated on the rats while feeding. In
the treated rats, bugs expressed signs of intoxication such as
inconsistent movements, unfolding of the rostrum, swelling of
the abdomen and shiny cuticle. It is important to note that no
blood was observed when a needle was pressed into the swollen
abdomen in such bugs. In treated rats, the proportions of fed bugs
were 3.1, 15.0, 19.3, 18.1 and 55.0% on days 1, 7, 14, 21 and 28,
respectively (Table 1).

Fed bug counts were significantly lower for DPP-treated rats
than for untreated control rats (P < 0.0001) at all time-points.
The anti-feeding efficacy of DPP was high at 96.7, 84.7, 80.5
and 81.5% on days 1, 7, 14 and 21, respectively, and decreased
to 42.6% on day 28 (Table 2). At 1 and 24 h post-exposure, the
AMs of live bugs were significantly lower for DPP-treated rats
than for untreated control rats (P < 0.0001) throughout the study
(Table 2). Insecticidal efficacy evaluated at 1 h after exposure
ranged between 80.0 and 100% up to day 21 and declined to
29.1% at 28 days after treatment, whereas insecticidal efficacy
assessed 24 h after exposure remained above 96.0% until day 21
and declined to 49.9% at 28 days after treatment (Table 3).
No difference in treatment sensitivity was observed between adults
and instar nymphs.

**Discussion**

Animal models can provide preliminary and complementary
information that is useful in further testing on targeted animals.
In the present study, a rat model was selected to explore the
anti-feeding and insecticidal efficacy of DPP against T. infestans.
Previous studies have demonstrated the possibility of extrapolat-
ing the results obtained in mice treated with a mosquito repellent
to humans (Reifenrath & Rutledge, 1983; Rutledge et al., 1994).
Although representativeness can be questioned, the information
collected from the models is definitely useful in terms of opti-
mizing the designs of experiments in the target animals.

In the present study, the feeding rate of T. infestans on control
rats exceeded 94.0% at all five time-points tested (Table 1). This
strong feeding rate showed that the population of T. infestans
used in the experiment was robust and the challenge was reliable.
This is consistent with previous observations in experiments
conducted in Triatoma rubrofasciata fed on Swiss mice (Braga
& Lima, 1999) and T. infestans fed on Sprague–Dawley rats,
Table 1. Feeding and mortality rates in *Triatoma infestans* (12 nymph instars and four adults per rat) on rats untreated (control group; *n* = 10) and treated (*n* = 10) with a combination of dinotefuran, permethrin and pyriproxifen.

<table>
<thead>
<tr>
<th>Exposure day</th>
<th>Feeding rate, % (<em>n</em>)</th>
<th>Mortality rate, % (<em>n</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated group</td>
<td>Treated group</td>
</tr>
<tr>
<td>1</td>
<td>96.2% (154)</td>
<td>3.1% (5)</td>
</tr>
<tr>
<td>7</td>
<td>98.1% (157)</td>
<td>15.0% (24)</td>
</tr>
<tr>
<td>14</td>
<td>99.3% (159)</td>
<td>19.3% (31)</td>
</tr>
<tr>
<td>21</td>
<td>98.1% (157)</td>
<td>18.1% (29)</td>
</tr>
<tr>
<td>28</td>
<td>94.3% (151)</td>
<td>55.0% (88)</td>
</tr>
</tbody>
</table>

Table 2. Anti-feeding efficacy against *Triatoma infestans* (12 nymph instars and four adults per rat) on rats untreated (control group; *n* = 10) and treated (*n* = 10) with a combination of dinotefuran, permethrin and pyriproxifen.

<table>
<thead>
<tr>
<th>Exposure day</th>
<th><em>T. infestans</em> feeding, AM ± SD</th>
<th>Repellency efficacy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated group</td>
<td>Treated group</td>
</tr>
<tr>
<td>1</td>
<td>15.4 ± 0.8</td>
<td>0.5 ± 0.7</td>
</tr>
<tr>
<td>7</td>
<td>15.6 ± 0.6</td>
<td>2.4 ± 0.9</td>
</tr>
<tr>
<td>14</td>
<td>15.8 ± 0.3</td>
<td>3.1 ± 1.2</td>
</tr>
<tr>
<td>21</td>
<td>15.7 ± 0.4</td>
<td>2.9 ± 1.6</td>
</tr>
<tr>
<td>28</td>
<td>15.1 ± 1.1</td>
<td>8.8 ± 1.5</td>
</tr>
</tbody>
</table>

*Significant difference between the treated and untreated (control) groups (*P* < 0.0001).

AM, arithmetic mean; SD, standard deviation.

in which more than 86% of bugs were seen to bite the host (Canals *et al.*, 1999). The single topical treatment of DPP had an immediate effect after administration, as demonstrated by the high anti-feeding efficacy (> 80%) that started at day 1 and lasted until day 21 after treatment. The anti-feeding effect decreased to 42.6% at 28 days after treatment (Table 2). If such a decrease in efficacy were to be confirmed in dogs at the appropriate dose, DPP could be safely reapplied at 3-week intervals (Coussanes *et al.*, 2015). This anti-feeding performance were not observed in previous studies assessing the effects of deltamethrin-based collars (Reithinger *et al.*, 2005, 2009) or fipronil-(S)-methoprene spot-on treatment (Gürtler *et al.*, 2009) on dogs or with imidacloprid spot-on applied to pigeons (Carvajal *et al.*, 2014). This high level of anti-feeding efficacy of DPP can be explained by the synergistic action of dinotefuran and permethrin against insects at the tested ratio (Varloud *et al.*, 2015a, 2015b). The administration of DPP will prevent bugs from taking bloodmeals from treated animals (dogs) and is expected to reduce the transmission of *T. cruzi* to and from dogs, which are considered to represent the pathogen’s main domestic reservoir (Reithinger *et al.*, 2005, 2006; Amelotti *et al.*, 2012).

The feeding rates of *T. infestans* on DPP-treated rats at days 1, 7, 14, 21 and 28 were 3.1, 15.0, 19.3, 18.1 and 55.0%, respectively. These were lower than that reported in a previous dog study in which another insecticide (deltamethrin) of the second-generation pyrethroids was tested on dogs against *T. infestans* bugs using deltamethrin-impregnated dog collars (Reithinger *et al.*, 2005). The earlier results showed feeding rates of 97, 93, 91, 93 and 85% in dogs wearing deltamethrin-impregnated collars, and 99, 100, 97, 91 and 90%
in control dogs on days 0, 15, 30, 60 and 90, respectively. However, over the 90-day period, the average engorgement rate on collared dogs remained significantly lower at 30.8% compared with 55.2% on control dogs (Reithinger et al., 2005). Similar results were reported in another study in which the proportion of feeding bugs was significantly lower (92.2%) on collared dogs than on control dogs (95.1%) over the entire 126-day observation period (Reithinger et al., 2006). It is important to stress that the collars (i.e. impregnated with 40 mg/g deltamethrin) are effective for up to 6 months (Reithinger et al., 2006).

Survival rates of *T. infestans* on the untreated control rats were also satisfactory, with over 98 and 93% surviving until 1 and 24 h, respectively, after the end of the exposure period (Table 1). These data validate the level of challenge in the present study. Although the treatment was applied at the lowest recommended dose, DPP exhibited high insecticidal efficacy against the bugs. Efficacy exceeded 80.0% and 96.0% at 1 and 24 h post-exposure from day 1 and over the 21-day period, respectively. It declined to 29.1% and 49.9% at 1 and 24 h post-exposure on day 28, although mortality remained significant.

The combination of dinotefuran with permethrin at the ratio used in the DPP combination led to a synergistic effect, inducing a faster onset and residual killing activity against insects (Varloud et al., 2015b). The percentages of bugs that died at 24 h post-exposure on days 1, 7, 14, 21 and 28 after treatment in the treated group were 100, 100, 100, 96.2 and 50.6%, respectively. These were higher than the rate reported by Reithinger et al. (2006), who tested deltamethrin-based collars on dogs against *T. infestans*. Their results showed that 23.9% of bugs died over the entire 126-day observation period. The insecticidal effect of DPP was also higher than that reported for fipronil-(S)-methoprene spot-on for dogs tested against *T. infestans* (Gürtler et al., 2009). These authors’ results showed that cumulative mean bug mortality after exposure differed significantly only at 1 week after treatment, when mortality was 18.7% in bugs infesting dogs treated with fipronil-(S)-methoprene and 4.4% in bugs infesting control dogs. Another study conducted in both laboratory and field conditions tested the efficacy of liquid fipronil (1.0%) against *T. infestans* nymphs on dogs, chickens and goats. Its results showed nymphal mortality of 100% after 7 days and 88.8% after 30 days in the laboratory assessments, and a 65.4% decrease in triatomine density after 30 days in field experiments (Gentile et al., 2004). Even when applied as a spot-on in pigeons at a massive dose (158 mg/kg pigeon), imidacloprid did not provide insecticidal efficacy that lasted over 7 days after administration, although the exposure of bugs to the active ingredient (imidacloprid) was maximized by exposing the insects to the pigeons at the site of administration of the product (Carvajal et al., 2014). Data for the performance of DPP obtained in rats cannot be directly compared with data recorded for fipronil-(S)-methoprene or deltamethrin-based products used in dogs or with data for imidacloprid applied to pigeons. Such differences can be explained by both methodological and product effects. To the present authors’ knowledge, this is the first time that a dinotefuran-based combination has been tested against triatomine bugs. Dinotefuran is a fumigantinot belonging to the third generation of neonicotinoids and is known as a fast-acting insecticide (Wakita et al., 2005). When it is combined with permethrin, the effect of dinotefuran against insects is enhanced at the ganglionic synaptic level, resulting in increases in depolarization and desensitization (Varloud et al., 2015b). When cis-permethrin or deltamethrin were used alone against *T. infestans* nymphs, parasite recovery was observed (Alzogaray & Zerba, 1997). In the present experiments, the bugs did not recover. This lethal effect of DPP is assumed to be linked to the synergistic combination of dinotefuran and permethrin.

Despite the success in eliminating *T. infestans* from Uruguay, Chile and Brazil, triatomine bugs remain widespread and continue to pose serious problems in other countries of the Southern Cone of South America, such as Bolivia, Argentina, Paraguay and Peru. The species is almost exclusively domestic in all of these countries. In outbreaks, particularly in Argentina, where Chagas’ disease is transmitted by *T. infestans*, dogs and cats represent domestic reservoirs of *T. cruzi* infection (Cardinal et al., 2007). Levels of canine seroprevalence to *T. cruzi* are high in 15 countries and vary from 8 to 50% across various surveys, which are often conducted using different techniques (Barbosa-Piego et al., 2011; Berrizbeita et al., 2013; Chikweto et al., 2014; Tenney et al., 2014; Alroy et al., 2015; Gürtler & Cardinal, 2015; Saldaña et al., 2015). Dogs should be prevented from becoming infected by restraining their access to ecosystems that feature vector bugs. The protection of dogs using a residual insecticide applied as a spot-on treatment should be strongly recommended in high-risk areas. Studies in Argentina have helped to highlight the correlation between the

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**Table 3.** Insecticidal efficacy against *Triatoma infestans* (12 nymph instars and four adults per rat) on rats untreated (control group; *n* = 10) and treated (*n* = 10) with a combination of dinotefuran, permethrin and pyriproxyfen at 1 and 24 h post-exposure.

<table>
<thead>
<tr>
<th>Exposure day</th>
<th>Live <em>T. infestans</em>, AM ± SD</th>
<th>Insecticidal efficacy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 h Untreated group</td>
<td>Treated group</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>1.4 ± 1.2</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>2.8 ± 1</td>
</tr>
<tr>
<td>21</td>
<td>15.8 ± 0.4</td>
<td>3.3 ± 0.5</td>
</tr>
<tr>
<td>28</td>
<td>16</td>
<td>11.5 ± 2</td>
</tr>
</tbody>
</table>

*Significant differences between the treated and untreated (control) groups (*P* < 0.0001).

AM, arithmetic mean; SD, standard deviation.
number of infected dogs in homes and the number of human cases (Gürtler et al., 2005). Similarly, in Brazil, infection (both acute and chronic) of children is linked to that of dogs (Mott et al., 1978). This is why the prevention of blood feeding on dog hosts is a primary target in the fight against Chagas’ disease transmission to humans.

Conclusions

The present study demonstrates that at the dosages tested, DPP has reliable anti-feeding and insecticidal effects against T. infestans. Indeed, the anti-feeding effect of DPP against bugs may increase the risk to humans of contracting the parasite because if T. infestans is unable to feed on treated dogs, it will bite another host, such as a human. However, the powerful insecticidal efficacy of the product offsets this effect because it will reduce the population of bugs in homes, thus reducing insect bites to humans. On rats, these two efficacy parameters persisted at > 80% for at least 3 weeks after treatment and both actions were detected at significant levels for at least 1 month. Although such results require further investigation in the target species, the tested dose was designed to be representative of the minimal recommended dose in dogs. Consequently, these results are expected to represent a reliable estimate of the anticipated performance of DPP on dogs against triatomine bugs. The preventive treatment of non-infected dogs with DPP may protect them from contact with triatomines and reduce the risk for transmission of certain zoonotic agents to humans.

Acknowledgements

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DT conceived the study design, performed the experiments, carried out data analysis and interpretation and wrote the first draft of the manuscript. BD participated in the study design, the experiments and in the writing of the manuscript. JMB produced triatomines and participated in the revision of the manuscript. MV was involved in studying designing, interpreting data and revising the manuscript. LA participated in data analysis and revision of the manuscript. DR facilitated the implementation of the work. PP participated in the study design, in data analysis and critically revised the manuscript. All authors have read and approved the final version of the manuscript.

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Efficacy of DPP against bugs

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