Cross-resistance between macrocyclic lactones in populations of *Rhipicephalus microplus* in Brazil’s semiarid region

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**Abstract**

*Rhipicephalus microplus*, also known as the cattle tick, is the parasite with the greatest impact on cattle in Brazil. The most common method for controlling this tick is the application of synthetic chemical acaricides, especially ivermectin, which belongs to the group of macrocyclic lactones (MLs). However, because ivermectin is widely used, there is concern about the development of cross-resistance within this chemical class. Thus, engorged females were collected from farms with a history of resistance to ivermectin, which was the only one among the MLs that was used as an endectocide drug. Using larval immersion tests (LIT), bioassays were performed with ivermectin, moxidectin and eprinomectin on populations of *R. microplus* from the semiarid region of the states of Paraíba and Ceará, Brazil. Epidemiological questionnaires were applied to collect information about tick control management. All the evaluated populations showed cross-resistance between ivermectin and moxidectin, but only one population showed cross-resistance between ivermectin and eprinomectin. Weekly or monthly administration of injectable 1% ivermectin on farms was reported. It was concluded that the frequent use of ivermectin may lead to the development of cross-resistance to moxidectin. For eprinomectin, despite the structural similarity, cross-resistance was not observed in three tick populations.

**Keywords** Acaricides · Cattle tick · Eprinomectin · Ivermectin · Moxidectin

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Introduction

_**Rhipicephalus microplus**_ infests cattle in tropical and subtropical regions. Larva, nymphs and adults attach to and develop in a single host, characterizing its life cycle as monoxenous (Taylor, 2019). Although this tick is present throughout the year in Brazil, in the semi-arid region of the country’s northeast it reaches its peak during the rainy season, which tends to occur from January to May or June. In the dry season, _R. microplus_ hardly ever achieves high rates of oviposition and egg hatch. Thus, the semi-arid climate, with high temperature and low air humidity, negatively influences the life cycle of these ectoparasites (Barros et al., 2017). _Rhipicephalus microplus_ is the parasite that has the greatest impact on cattle, causing the transmission of several pathogens, including _Babesia_ spp. and _Anaplasma_ sp. (Costa et al., 2013). That is why the effective control of this ectoparasite is of utmost concern.

In Brazil, _R. microplus_ populations have developed resistance to all available acaricides (Reck et al., 2014; Rodiguez-Vivas et al., 2014; Valsoni et al., 2020, 2021; Villar et al., 2020). The excessive use of acaricides in the absence of knowledge about the life cycle of the arthropod, allied to failures in its detection and mismanagement in animal husbandry, has lead to the development of resistance to almost all classes of veterinary drugs, and the more widely these acaricides are applied, the higher the percentage of drug resistance (Kumar et al., 2020; Villarreal et al., 2021).

Since its discovery in 1980 (Chabala et al., 1980), ivermectin has been one of the most commonly used drugs in the treatment of _R. microplus_ infestations. Ivermectin belongs to the group of macrocyclic lactones (MLs), which is composed of avermectins (ivermectin, eprinomectin and doramectin) and milbemycins (moxidectin). The substances are naturally produced by _Streptomyces avermitilis_ (Brossi, 2018). Macrocyclic lactones act as an analogue of the neurotransmitter γ-aminobutyric acid (GABA) and in GluCl. By binding to chlorine channels, they cause the uninterrupted influx of Cl⁻ ions into neurons at the neuromuscular junction, blocking neurotransmission. Thus, they paralyze the tick’s somatic and pharyngeal muscles (Omura, 2008).

The first report of resistance to ivermectin in the tick _R. microplus_ (São Gabriel strain) in Brazil was described by Martins and Furlong (2001). Since then, several studies have shown the occurrence of this resistance in different locations (Klafke et al., 2006, 2012; Andreotti, 2010; Lopes et al., 2013; Vilela et al., 2020). In addition, Martins and Furlong (2001) reported cross-resistance between doramectin, moxidectin and ivermectin in studies carried out with the São Gabriel strain. However, the existence of cross-resistance to eprinomectin and moxidectin has not yet been reported in field populations, although ticks showed susceptibility in laboratory experiments (Nazir et al., 2013; Nascimento et al., 2020). However, in studies with moxidectin conducted by Lovis et al. (2013), the population of _R. microplus_ on a farm in Argentina proved to be resistant, although this trial was not replicated, as the authors point out themselves. In Brazil, these two compounds are used only occasionally, and the use of ivermectin is more widespread.

Due to the drug resistance of _R. microplus_, particularly against ivermectin, there is a concern about the possibility of cross-resistance between MLs, given their similar molecular structures and mechanisms of action. Therefore, this work aimed to evaluate the existence of cross-resistance between MLs in _R. microplus_ populations in the semi-arid region of Northeast Brazil, based on in vitro larval bioassays.
Material and methods

Collection of samples and location of experiments

Samples were collected at four cattle farms in Brazil’s northeast semiarid region, covering the municipalities of São João do Rio do Peixe—PB (Farm 1), Sousa—PB (Farm 2), Barro–CE (Farm 3) and Várzea Alegre—CE (Farm 4) (Fig. 1). Farms were selected based on their history of using ivermectin as an acaricide and the resulting resistance.

The experimental tests were carried out at the Veterinary Parasitology Laboratory of the Federal Institute of Paraíba—IFPB at the city of Sousa.

Characterization of the farms

In order to build a profile of the farms, a questionnaire was applied containing the following items: bovine population, breed of animals, production system (intensive, extensive or semi-intensive), main purpose (dairy or beef cattle), and size of grazing area. For a tick management profile, the following information was asked for: acaricides applied in the last 2 years, acaricide applied in the last treatment before ticks were collected, interval between treatments, performance of treatments according to the manufacturers’ recommendations, application method (spray, injectable or pour-on formulations), and influence for the choice of a specific acaricide: recommended by a veterinary doctor, veterinary pharmaceutical sales representatives, by neighbors/cooperatives, or determined by product price. Given the endectocide action of the LMs, also information about helminth control was collected.

Fig. 1 Location of the farms of the field populations analyzed in the Northeastern semiarid region of the states of Paraíba and Ceará, Brazil
Ticks

Since it was first isolated, the Porto Alegre (POA) strain has been widely used as a susceptible reference strain (Reck et al., 2014; Vilela et al., 2020). The POA isolate was kept in a BOD (bio-oxygen demand) incubation chamber, keeping temperature at 28 °C and relative humidity above 80%, later being used as a susceptible strain of reference.

Approximately 100 engorged females were collected at each farm from cattle that had been treated with topical acaricide at least 30 days earlier, or 45 days after treatment with injectable acaricide, to ensure the absence of interference in the results. Ticks were removed directly from infested cattle and placed in plastic containers (10.5 cm high, 8 cm diameter) with holes in the lid to allow the passage of air. The containers were kept in a polystyrene box until their arrival at the Veterinary Parasitology Laboratory (LPV) of the Federal Institute of Paraíba (IFPB) at Sousa. At the laboratory of IFPB, ticks were processed as specified by FAO (2004). The ticks were washed in distilled water, dried on paper towels, placed on plastic Petri dishes (9 cm diameter, 2.2 cm high) and incubated in a BOD chamber in the dark, at 27–28 °C and 85–90% RH. Female ticks were left in the BOD chamber for 2 weeks, giving them time to lay eggs. Egg masses (250 mg aliquots) were then placed in glass vials (10 mL), which were closed with a cotton lid, allowing air and moisture to pass through. To enable the larvae to hatch, the eggs were incubated under the same conditions as the engorged females.

Acaricides

Technical grade ivermectin, eprinomectin and moxidectin was used (Sigma Chemical, St. Louis, MO, USA).

Larval immersion test (LIT)

Acaricides were diluted in 2% Triton X-100 solution in absolute ethanol (ETH-TX2%) in the case of eprinomectin and 2% Triton X-100 with pure acetone (ACTX-2%) in that of ivermectin and moxidectin dilution. The solutions for dilution were different to ensure a more homogeneous dilution of the acaricides. Ivermectin, eprinomectin and moxidectin were evaluated with the larval immersion test (LIT), as described by Klafke et al. (2012). A diluent without acaricide was used as a control for all acaricides.

The bioassay was performed using 500 μL of each immersion solution distributed in three 1.5 mL microcentrifuge tubes. Using a brush, approximately 100 larvae were transferred to each tube, which was then closed and shaken vigorously to ensure the larvae were completely submerged. After 10 min of immersion, the larvae were removed from the tube with a clean brush, allowed to dry on a paper towel, then transferred to a filter paper package folded in half and closed on the sides with metal clips. After adding the larvae, the package was sealed with a third clip and incubated in the dark in an environmental chamber at 27–28 °C and 85–90% RH. After 24 h, larval mortality was determined by counting all live and dead individuals. Larvae that were paralyzed or that moved only their appendages, but unable to walk, were considered dead.
Statistical analysis

Probit analysis was performed on the bioassay results, using Polo-Plus software (LeOra Software, 2003). The following parameters were estimated for each test: LC\textsubscript{50} (50% lethal concentration) with its 95% confidence interval (95% CI) and the slope of the regression line. Resistance was calculated based on a comparison of the susceptibility of the field population and the susceptible reference strain, determining the LC\textsubscript{50} for each field population and the LC\textsubscript{50} for the POA strain.

Results

The four visited farms had an average stocking rate of 2.1 animal unit/ha, with areas of native Caatinga pasture and areas with cultivated grasses (\textit{Pennisetum purpureum} and \textit{Cenchrus ciliaris}). The average population of the herds was 123 (52–200) cattle. Two farms (1 and 3) are exclusively dairy, whereas the others have mixed production (beef and dairy). Farms 1 and 3 had Holstein cattle, farm 2 had Holstein and Gyr breeds, and farm 4 had crossbred cattle.

The main health problems reported on the farms were tick infestations (farms 1, 3 and 4), whereas the main problem reported on farm 2 was the occurrence of cattle fever tick. The farms have a history of using sprays and pour-on with synthetic and organophosphate pyrethroids to control ticks. However, the most frequent administration is by injection, with weekly or monthly application of 1% ivermectin to control \textit{R. microplus} and/or \textit{Haematobia irritans}. Farmers stated they had never administered eprinomectin and moxidectin against endo- or ectoparasites to their animals. In all farms, there was no specific control for deworming, with the secondary administration of ivermectin to control the tick. On all farms, the control of \textit{R. microplus} started when the producers noticed the effect of telegony in the animals.

All \textit{R. microplus} populations showed resistance to ivermectin when compared with the POA strain (Table 1). Ivermectin presented a resistance factor (RF) ranging from 6.3 to 38.9. Only the Barro-CE population demonstrated resistance to eprinomectin (RF = 31.4). Moxidectin presented RF values ranging from 5.6 to 339.2 (Table 1).

All populations showed cross-resistance between ivermectin and moxidectin. However, only in the Barro-CE population collateral resistance between ivermectin, eprinomectin and moxidectin was shown.

Discussion

The farms visited in this study engage in practices that are known to predispose to the development of acaricide resistance, such as high animal stocking rate, dairy production and predominance of taurine breeds (Utech et al., 1978; Veríssimo et al., 2002; Vilela et al., 2020). Pereira et al. (2010) reported that inadequate management of acaricides—including incorrect application, continuous use of spray formulations, high frequency of treatments, initiation of treatments only after the discovery of engorged female ticks, and incorrect interval between treatments—facilitate the development of
drug resistance. These practices were also observed on all the farms that participated in this study.

It was found that ivermectin was the only macrocyclic lactone used on the farms, and that the animals never received treatments with eprinomectin and moxidectin. However, resistance to the acaricides ivermectin, eprinomectin and moxidectin was observed in one tick population, and to ivermectin and moxidectin in the other three populations studied. Thus, it is evident that cross-resistance can occur between acaricides of the same group.

We highlight the importance of adopting strategies to control cattle ticks in the Brazilian semiarid region, mainly due to overuse of macrocyclic lactones, as observed by Vilela et al. (2020).

Given their similar structural formulations and mechanisms of action, high cross-resistance between ivermectin and eprinomectin (avermectins) was expected, as they are amino-avermectins derived from avermectin B1, which have a modified terminal olean-drose moiety called 400-deoxy-400-epi-acetylamino-avermectin B1. However, cross-resistance between these drugs was only observed in the Barro-CE population. In studies with nematodes, Ménez et al. (2016) demonstrated that with the multidrug-resistant phenotype selected by ivermectin and moxidectin, the nematodes were also more resistant to eprinomectin than the wild-type strain (eprinomectin being the less potent drug after ivermectin and moxidectin selection pressure). Thus, further studies are needed to better characterize the resources the tick *R. microplus* uses to build up its eprinomectin resistance.

Acaricide resistance may be metabolic—via an increase in the detoxification ability of the acaricide--; by structural alterations in the exoskeleton, leading to reduced penetration of acaricides; or molecular, involving target-site mutation, the latter being described in ivermectin-resistant populations (Pohl et al., 2012; Guerrero et al., 2013).

### Table 1 Cross-resistance status of *Rhipicephalus microplus* populations in the states of Paraíba and Ceará, Brazil, using the larval immersion test (LIT)

| Farm         | Population | Treatment | No. | Slope (SE) | LC$_{50}$ (95% CI) | RF |
|--------------|------------|-----------|-----|------------|--------------------|----|
| –            | POA        | IVM       | 2087| 2.865 (0.154) | 26.228 (15.368–39.439) | – |
|              |            | EPM       | 2006| 3.541 (0.178) | 22.439 (15.998–31.032) | – |
|              |            | MOX       | 2788| 10.454      | 0.297 (0.281–0.313)    | – |
| 1            | S. J. Rio do Peixe—PB | IVM | 1473| 1.447 (0.094) | 167.214 (146.189–263.727) | 6.375 |
|              |            | EPM       | 2306| 3.445 (0.177) | 5.277 (4.814–5.754)    | 0.235 |
|              |            | MOX       | 2700| 1.338 (0.060) | 100.748 (65.928–143.057) | 339.281 |
| 2            | Sousa—PB   | IVM       | 3383| 1.305 (0.052) | 1021.235 (725.243–1525.858) | 38.936 |
|              |            | EPM       | 1855| 0.911 (0.047) | 12.434 (7.267–18.950)  | 0.554 |
|              |            | MOX       | 3297| 4.985 (0.312) | 2.957 (2.712–3.201)    | 9.956 |
| 3            | Barro—CE   | IVM       | 2478| 1.105 (0.039) | 221.170 (153.254–329.165) | 8.432 |
|              |            | EPM       | 1713| 0.958 (0.047) | 705.417 (473.761–1141.840) | 31.437 |
|              |            | MOX       | 2400| 7.870 (0.866) | 6.789 (5.584–7.731)    | 22.888 |
| 4            | Várzea Alegre—CE | IVM | 2407| 3.105 (0.212) | 527.093 (234.052–782.235) | 20.096 |
|              |            | EPM       | 1582| 0.620 (0.052) | 1.308 (0.201–3.711)    | 0.058 |
|              |            | MOX       | 2288| 5.057 (0.272) | 1.688 (1.593–1.784)    | 5.683 |

*POA* susceptible Porto Alegre reference strain; *IVM* ivermectin; *EPM* eprinomectin; *MOX* moxidectin; No. number of larvae used in the tests; SE standard error; LC$_{50}$ lethal concentration for 50% of the population; 95% CI, 95% confidence interval; RF resistance factor (= LC$_{50}$ test population/LC$_{50}$ POA)
Despite the similarities between macrocyclic lactones, there are important differences between ivermectin and moxidectin, such as plasma and tissue kinetics. Moxidectin can long maintain activity (150 days) in different long-acting formulations, such as the drug Cydectin 10% LA (Zoetis, Louvain-la-Neuve, Belgium). According to Prichard et al. (2012), when resistance to avermectins first develops, it usually influences the effectiveness of all avermectins. However, as a milbemycin, moxidectin is generally still highly effective against avermectin-resistant parasites at its recommended dose rate. According to Ranjan et al. (2002), parasite resistance to moxidectin develops more slowly than to ivermectin. However, the findings of this study suggest that resistance to moxidectin may occur as a result of continuous high selection pressure through the use of ivermectin.

Observing and comparing the RF of the tick populations, it can be stated that there may be different types of receptors and/or existing connections. These differences in the responses to ivermectin and eprinomectin suggest that there are differences in the level of interaction of GluCl with these molecules, or that the involvement of other amino acid-restricted chlorine channels with the actions of avermectins and moxidectin differ, as suggested by Lespine et al. (2012) in their studies with nematodes.

Conclusions

In view of the findings of this study, it can be stated that *R. microplus* populations from Brazil’s northeastern semiarid region exhibit collateral resistance between the macrocyclic lactones ivermectin and moxidectin, which may be caused by selection pressure, favored by the long-term use of ivermectin. However, although eprinomectin is structurally similar to ivermectin, this type of resistance was not observed.

Author contributions All the authors contributed to the conception and design of the study. Material preparation, data collection and analysis were carried out by LCF, EFL, ALPS, CSMO, GMSF, LCS, GMK, TFF and VLRV. The first version of the manuscript was written by LCF, GMK and VLRV; and all the authors made comments in previous versions of the manuscript. All the authors read and approved the final manuscript.

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Data availability Datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare that they have no conflict of interest relevant to the content of this article.

Ethical approval The activities involved in this research were approved by the Ethics Committee for Animal Use of our institution (CEUA/IFPB), under protocol number 23000.000558.2021–23.

Consent to participate Not applicable.
Consent for publication Not applicable.

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