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Miltefosine assay in the saliva of dogs treated with an oral suspension containing miltefosine 2%

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Background

Canine leishmaniosis due to *Leishmania infantum* is a major global zoonosis potentially fatal. The complexity of this zoonotic infection and the wide range of its clinical manifestations, from subclinical to severe disease, make the management of canine leishmaniosis challenging. [1] In order to ensure the safe use of the product by veterinarians and pet owners, a quantitative user safety assessment has been conducted, taking into consideration exposure scenarios such as hand contact or licking by treated dogs. The objective of this study was to determine miltefosine concentrations in the saliva of dogs after oral administration of a commercial veterinary oral suspension containing miltefosine 2% (20mg/mL) for 28 consecutive days and up to one month after the treatment arrest.

Materials and methods

The design of the study received a favourable opinion from the ethics committee and was accepted by the competent authority. Under Good Laboratory Practices, a total of 10 conventional beagle adult dogs (4 males and 6 females, 8-15 kg body weight) were orally dosed once per day with a commercial veterinary oral suspension containing miltefosine 2% at the dosage of 0,1 mL per kg body weight per day (equivalent to 2 mg miltefosine per kg per day). Animals received the treatment during 28 consecutive days from Day 0 to Day 27. A portion of food was distributed approximately 30 minutes before treatment and the rest of the ration was distributed within 2 minutes after treatment. Animals were observed regularly for clinical examinations. During the 28-day treatment period, saliva was regularly sampled on gauze pads before each administration, 5- and 15 minutes post-administration and 4- and 8 hours post-administration. During the post-treatment period until day 55, saliva samplings were also thoroughly performed. Saliva samples were analysed for miltefosine residues using a validated UHPLC-QDa method (Ultra High-performance Liquid chromatography with QDa Detection).

Results

Clinical examinations revealed gastrointestinal manifestations (soft stools) mostly during the treatment period, without any degradation of general status, any signs of discomfort or any loss of appetite. These observations are known to be commonly associated with the miltefosine administration. During the treatment period, miltefosine residues in saliva were maximal 5 minutes after the administration, with the highest individual levels dosed at 224.9 µg/gauze pad. The miltefosine residues decreased from 15 minutes post-administration. Each day, the kinetic of the miltefosine concentrations in saliva were similar. The salivary concentration of miltefosine at 5 minutes, 15 minutes and 4 hours post-administration on the first day of treatment is presented in Figure 1. No tendency of increase or accumulation has been seen. Immediately after the end of administration, residues of miltefosine in saliva decreased rapidly from D28 to being non-quantifiable from D31 and were presented in Figure 2.

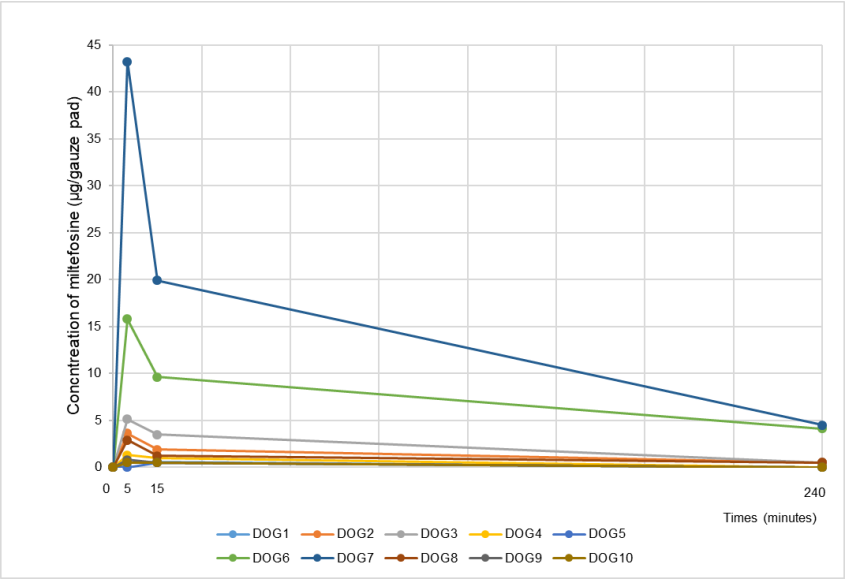

Figure 1. Salivary concentration of miltefosine at 5 minutes, 15 minutes, and 4 hours after the first administration (Day 0)

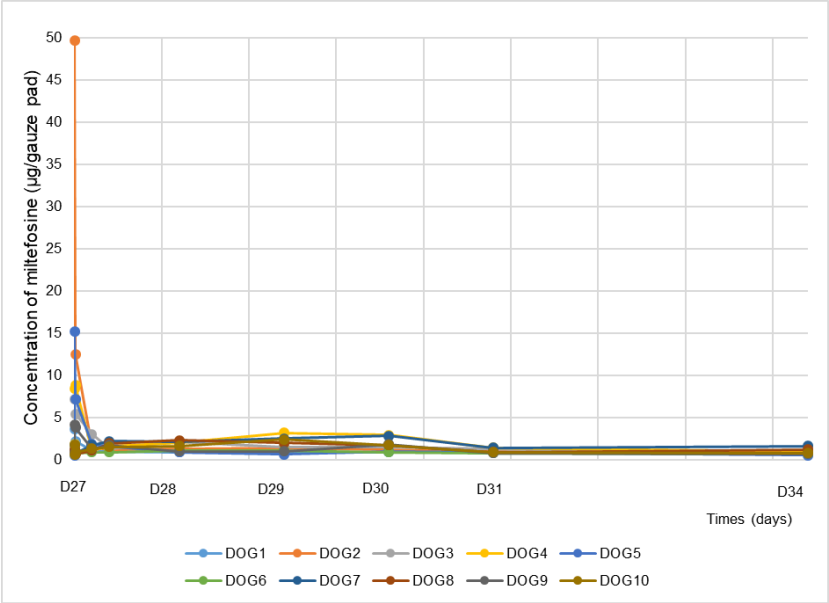

Figure 2. Salivary concentration of miltefosine from the last day of administration (Day 27) until the end of the observation period (up to Day 34)

Conclusions

The results obtained in this study reflect saliva content in terms of miltefosine residues when dogs are treated against canine leishmaniosis with the commercial veterinary oral suspension containing miltefosine 2% (20mg/mL). In these conditions, dogs had the maximal level of residues in saliva within 5 minutes post-administration with no tendency of increase or accumulation. The level of residues in saliva remained low during the administration period and was non-quantifiable from 3 days after the last administration. The results of this study were used in the user risk assessment of the commercial veterinary oral suspension containing miltefosine 2%. This study established the low user risk when dogs received a canine leishmaniosis treatment based on miltefosine under the recommendation of the Summary of Product Characteristics.

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Conflict of interest: information not provided by the authors.

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