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Miltefosine assay in plasma, urine and faeces 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. Current treatment protocols for canine leishmaniosis include the administration of miltefosine [1]. The aim of this study was to evaluate the miltefosine assay in plasma, urine and faeces in dogs receiving a 28-day oral repeated administration of a commercial veterinary oral suspension containing miltefosine 2% (20 mg/mL).

Materials and methods

The design of the study received a favourable opinion from the ethics committee and was accepted by the competent authority. Six conventional Beagle dogs received an oral dose of a commercial veterinary oral suspension containing miltefosine 2% at a dose rate of 2.0 mg per kg per day for 28 consecutive days. Blood specimens were collected before and at defined intervals after the first, the seventh, the fourteenth and the last treatment. Urine and faeces were collected daily over 10 days after the last administration. The concentration of miltefosine in dog plasma, urine and faeces was determined using a validated HPLC MS/MS (High-Performance Liquid Chromatography coupled to Mass Spectrometry) method.

Results

Gastrointestinal signs (vomiting and diarrhoea) were observed in all dogs until the 14th day, which was associated with a reduction of wet food intake. A shift to pelleted food resolved the situation, with a return to a normal health condition, with no additional clinical signs. After the first administration, the mean maximum plasma concentration (Cmax) obtained was 5 230 ± 655 ng/mL with a Tmax (time to reach observed Cmax) of 6 hours. After the last administration, the mean Cmax reached 32 582 ± 4 030 ng/mL with a mean Tmax of 5 hours. The mean Cmax and Tmax are presented in Table 1. An accumulation of about a 6-fold concentration increase (R = 6.4 ± 1.6) of miltefosine in dog plasma after repeated oral administrations for 28 consecutive days was observed. The mean terminal half-life of elimination ($T_{1/2}$el) of miltefosine calculated from the 28th administration was 148.5 hours. The long-observed $T_{1/2}$el (between 127 and 166 hours) is displayed in Figure 1. Faeces and urine collected over 10 days after the last administration showed that miltefosine was mainly excreted in the faeces. The individual concentration of miltefosine in urine remained below the lower limit of quantification at the majority of the collection periods.

Table 1. Mean Tmax and mean Cmax of miltefosine after oral administration in dogs.

Time	**Mean Cmax** (ng/mL) ± SD	**Mean Tmax** (h) ± SD
After 1st administration	5 230 ± 655	6.0 ± 0.0
After 7th administration	15 913 ± 3 201	5.2 ± 1.3
After 14th administration	22 368 ± 2 432	4.7 ± 2.0
After 28th administration	32 582 ± 4 030	5.0 ± 2.0

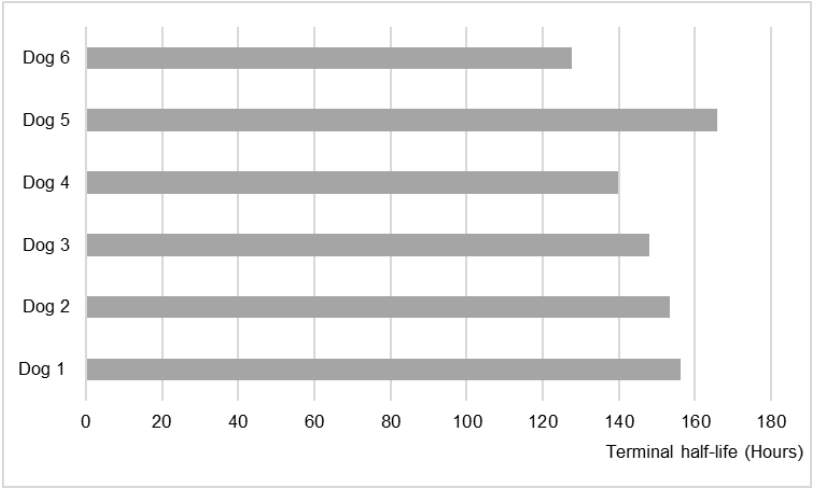

Figure 1. Terminal half-life of elimination of miltefosine calculated after the 28th oral administration in each dog.

Conclusions

This study showed that after an oral administration of a commercial veterinary oral suspension containing miltefosine 2%, miltefosine is rapidly absorbed, with a Tmax between 4.7 and 6.0 hours. The plasma clearance of miltefosine was very low which is illustrated by the long-observed terminal half-life. Due to the unique pharmacokinetics properties of miltefosine, the systemic exposure “loading phase” is progressive over the selected dosing interval (24 hours) during the repeated administrations. This progressive accumulation up to a steady state observed at 28 days is believed to favourably contribute to a time-dependent development of tolerance (progressive reduction of nausea and vomiting). Miltefosine is mainly excreted in the faeces. This absence of renal clearance is a very interesting property for a drug indicated to manage canine leishmaniosis, a disease often associated with renal disorders in dogs.

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