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In vitro human skin absorption of a commercial veterinary drug 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 administration of miltefosine [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 *in vitro* study was to evaluate the rate of skin absorption of miltefosine after the application of a commercial veterinary oral suspension containing miltefosine 2% (20mg/mL) on isolated human skin.

Materials and methods

Human dermatomed skin samples from 4 donors were provided by the bank of tissue of Lyon or Montpellier in France (Alphenyx, Biopredic, Tissue Solutions or private hospitals). Miltefosine skin absorption was assessed using Franz diffusion cells according to OECD Guidelines (Organisation for Economic Cooperation and Development) and under Good Laboratory Practice conditions. The miltefosine concentration was measured in 5 compartments: amount washed off the skin (skin excess), in the stratum corneum (strips), in the epidermis, in the dermis, and over time in the receptor fluid. There were 2 replicates per donor (total of 8 cells). The static cells with a donor chamber and a receptor chamber separated by the skin correspond to an application area of 2 cm^3. The product, a commercial veterinary oral suspension containing miltefosine 2% (20mg/mL), was applied homogeneously on each skin sample at 20 µL/cell, corresponding to a total amount of miltefosine applied of 400 µg/cell. Miltefosine concentration in the receptor fluid was assessed with a validated and calibrated analytical LC-MS/MS (Liquid Chromatography with tandem Mass Spectrometry) method. The experiment started immediately after application on the skin surface. Gentle washing of the skin surface and rinsing of the donor compartment was performed to measure the “skin excess” fraction. The stripping of the stratum corneum corresponded to a maximum of 15 strips per skin sample. Stripping was stopped if stripping induced separation of the epidermis and dermis. The total volume of receptor fluid was collected at around 1, 2, 4, 6, 8, and 24 hours after the application and precisely weighed.

Results

For each cell (n=8), the total compound recovery values for the 5 compartments analyzed were between 95.47% and 101.86% (within the acceptability range of 100±20%), with a mean value of 98.54% (± 2.23).
The results of Miltefosine cutaneous distribution expressed as % of applied dose are presented in Table 1. The dermal penetration of Miltefosine was quantified in the receptor fluid, except for only 2 cells out of 8, 24 hours after the application. A mean total absorption value (Strips 3-15 + Epidermis + Dermis + Receptor fluid +) of 0.95% (± 0.80) was calculated.

Table 1. Distribution in all compartments of the applied dose of Miltefosine 2% (n=8)

Compartment		Percentage of distribution (mean ± SD)
Skin excess		96.98 ± 2.99
Stratum corneum	(Strips 1-2)	0.60 ± 0.46
	(Strips 3-15)	0.24 ± 0.09
Epidermis		0.67 ± 0.69
Dermis		0.11 ± 0.13
Receptor fluid		0.02 ± 0.06
Total absorbed (Strips 3-15 + Epidermis + Dermis + Receptor fluid)		**0.95 ± 0.80**
Total recovery		**98.54 ± 2.23**

Conclusions

The rate of skin absorption of miltefosine after application of a commercial veterinary oral suspension containing miltefosine 2% was tested on 4 donor human skin samples tested in duplicate. The rate of skin absorption was very low, with a mean total absorbed percentage of 0.95% of the applied dose. The results of this study were used in the user risk assessment of the commercial veterinary oral suspension containing miltefosine 2%, when dogs received a canine leishmaniosis treatment based on miltefosine under the recommendation of the Summary of Product Characteristics.

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References

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