Comparative pharmacokinetics of ivermectin after its subcutaneous administration in healthy sheep and sheep infected with mange

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It is well established that the efficacy of any anthelmintic drug depends not only on its affinity for specific parasite target sites but also on its ability to reach high and sustained drug concentrations where the parasites are located.

Ivermectin is one of the most useful anti-parasitic agents. It belongs to the family of avermectins that are highly lipophilic macrocyclic lactones. It is a fermentation product of *Streptomyces avermitilis*. One of the most important characteristics of ivermectin is its wide spectrum of activity involving endo- and ectoparasites.

Ivermectin is effective when it is applied orally, parenterally or topically. Its absorption is rapid by any of these routes of administration (Campbell, 1989, 1993).

Mange is an ectoparasitic disease produced by the mite *Psoroptes ovis*. It has major economic importance in South America, especially Argentina, Chile and Uruguay. It is anticipated that in the diseased animal there are kinetic modifications largely dependent on the change of body condition. The objective of the present paper was to determine the pharmacokinetic changes of ivermectin when applied subcutaneously to healthy animals and animals carrying natural mange infections.

Six adult and healthy sheep (weighing 50 ± 6 kg) and five sheep naturally infested with psoroptic mites and showing mange lesions on at least 30% of their body surface (weighing 43 ± 6 kg) received 200 μg/kg ivermectin subcutaneously, the sampling times being at the following post-administration days: 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15, 18, 20, 25 and 30. Plasma was separated by centrifugation and kept frozen at −20 °C until assayed. Assay was performed by high-performance liquid chromatography (HPLC). The recovery was 85% and the quantitation limit was 0.1 ng/mL. Variability was lower than 8%. The HPLC system was a Shimadzu LC-10 AS pump and TM III 1311 model fluoromonitor. The column was a C8 reverse phase lichrospher and the mobile phase was glacial acetic acid/methanol/acetonitrile (9:200:291 mL) at a flow rate of 1.5 mL/min. Reagents were HPLC grade. Extraction was accomplished by the solid–liquid method with C18 cartridges. The eluate was evaporated, derivatizated and injected into the HPLC system (Alvinerie *et al.*, 1987). Pharmacokinetic analysis was performed by a linear regression program known as Estrip (Brown & Manno, 1978). Pharmacokinetic parameters were obtained following Baggot (1977) and Gibaldi and Perrier (1975). Statistically significant differences were considered with a probability <0.05 by using Student's *t*-test after log transformation of the data.

Figure 1 shows the mean plasma concentration–time curve of ivermectin in healthy and infested sheep. In Table 1, a comparison between the mean pharmacokinetic parameters of ivermectin in healthy and diseased sheep is shown. A one-compartment open model with first-order absorption was used to describe plasma kinetics. Maximum plasma concentration (C_{max}) was collected earlier in sheep infected with mange (T_{max} 0.90 days) than in healthy sheep (T_{max} 2.67 days), C_{max} was higher in sheep infected with mange (41.21 ng/mL) than in the healthy group (24.09 ng/mL). Comparing areas under the concentration–time curves, there were no statistically significant differences between sheep infected with mange (179.96 ng d/mL) and the healthy group (207.47 ng d/mL), probably because the group sizes were too small to pick up a potential difference; however, the healthy animals showed a higher mean value. There were no statistically significant differences between elimination half-lives in normal and diseased animals.

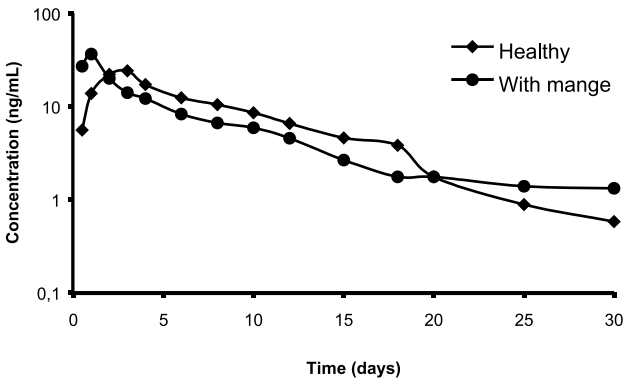

Fig. 1. Mean plasma concentrations of ivermectin vs. time curve in healthy sheep and sheep naturally infected with mange.

Parameters	Healthy	With mange	*P*-values
$T_{½ab}$	0.85 ± 0.62	0.24 ± 0.19	0.0330*
β (d − 1)	0.13 ± 0.03	0.15 ± 0.05	0.4169
$T_{½β}$ (days)	5.57 ± 1.25	5.54 ± 1.44	0.4883
C_{max} (ng/mL)	4.09 ± 6.57	41.21 ± 16.23	0.0206*
T_{max} (days)	2.67 ± 0.52	0.90 ± 0.22	2.933E-05*
AUC (ngd/mL)	207.47 ± 46.54	179.96 ± 90.59	0. 1781
$V_{d\ area}$ (L/kg)	8.76 ± 2.61	6.54 ± 1.72	0.0694
MRT (days)	8.61 ± 0.68	6.68 ± 1.83	0.0555

Table 1. Mean ± SD pharmacokinetic parameters of ivermectin in healthy sheep compared with those obtained in diseased sheep

$T_{½ab}$: absorption half-life ($0.693/K_{ab}$); β: slope of the elimination phase of the SC (subcutaneous) drug-disposition curve; $T_{½β}$: elimination half-life ($0.693/β$); C_{max}: maximum observed plasma IVM (ivermectin) concentration; T_{max}: time at which the maximum concentration occurred; AUC: area under the plasma IVM concentration–time curve; MRT: mean residence time; *P*: probability. *Statistically significant results at the 0.05 concentration.

Absorption was faster in animals with mange. C_{max} was higher and T_{max} was shorter. These values are probably related to the change in the body condition of the animals infected with mange. These animals were in poor body condition and showed a reduction of body fat. It is well known that avermectins are lipophilic molecules, which distribute extensively into organic lipids. This is the cause of a high V_d. The animals with mange, with less lipids in the body, showed a lower V_d for ivermectin with the simplistic approach used. A higher plasma affinity for the drug (because of less lipids in the body) gave rise to a higher C_{max} and a shorter T_{max}, indicating less transference to a smaller peripheral compartment. Although C_{max} was lower, the slow transference of the drug to and from tissues, and a larger V_d generated a much higher AUC in healthy animals. Consequently, although not statistically significant, ivermectin is more bioavailable in healthy sheep than in sheep with mange. Mean residence time was longer in healthy animals, which is a logical finding considering body condition.

Considering only the last four or five measured ivermectin concentrations, however, the slope of the curve obtained in the diseased animals was slightly less pronounced than that obtained in the healthy animals.

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Errata

Echeverría, J., Mestorino, N. & Errecalde, J.O. (2002) Comparative pharmacokinetics of ivermectin after its subcutaneous administration in healthy sheep and sheep infected with mange. *Journal of Veterinary Pharmacology and Therapeutics*, **25**, 159–160.

In this paper, the C_{max} value in the healthy column was incorrectly reproduced. The correct version is below.

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Bousquet-Mélou, A. & Toutain, P.L. (2002) Letter to the Editor. *Journal of Veterinary Pharmacology and Therapeutics*, **25**, 239.

In this paper, Equation 6 was incorrectly reproduced. The correct version is below.

$$AUC_{free,\max} = \frac{\frac{\dot{Q}_h}{fu \times Cl_{\text{int},h}} \times Dose}{\frac{\dot{Q}_h}{fu}} = \frac{Dose}{Cl_{\text{int},h}}$$