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Comparison of the Pharmacokinetics of Moxidectin and Ivermectin after Oral Administration to Beagle Dogs

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ABSTRACT: This study compares plasma disposition kinetics of ivermectin and moxidectin after oral administration to beagle dogs experimentally infected with the filarial parasite, *Brugia pahangi*. Sixteen dogs were selected and randomly allocated into two groups of eight dogs each. Animals in each group received either ivermectin or moxidectin by oral route at a dose of 250 μg/kg. Blood samples were collected from 0.5 h up to 56 days post-treatment and the plasma was analysed by high performance liquid chromatography (HPLC). The obtained data were analysed by compartmental and non-compartmental pharmacokinetic techniques. Peak plasma concentrations (C_{max}) of 234.0 ± 64.3 ng/ml (mean ± SD) were obtained for moxidectin and 132.6 ± 43.0 ng/ml for ivermectin. The terminal elimination half-life was significantly ($p < 0.01$) longer in the moxidectin treated group (621.3 ± 149.3 h) than for ivermectin treated group (80.3 ± 29.8 h). A significantly ($p < 0.01$) larger V_{ss}/F was obtained for moxidectin (19.21 ± 3.61 l/kg) compared with ivermectin (5.35 ± 1.29 l/kg). The mean estimates of CL/F of moxidectin and ivermectin were 0.0220 ± 0.00381 and 0.0498 ± 0.01791/h/kg, respectively. The comparative plasma disposition kinetics of ivermectin and moxidectin in dogs is reported for the first time. Copyright © 2007 John Wiley & Sons, Ltd.

Key words: ivermectin; moxidectin; pharmacokinetics

Introduction

The avermectins and milbemycins are derivatives of 16-membered macrocyclic lactones. Both groups are produced by soil dwelling actinomycetes, *Streptomyces* spp and share some structural and physiochemical properties. These two groups differ structurally mainly in a disaccharide group, present in the avermectins and absent in the milbemycins [1]. Ivermectin (Figure 1a), a semisynthetic derivative of the natural avermectins, contains at least 80% of 22–23 dihydroavermectin B1a and less than 20% 22–23 dihydroavermectin B1b. Ivermectin is a large highly lipophilic molecule and despite possessing two sugar rings and two hydroxyl groups is relatively insoluble in water [2]. Moxidectin (Figure 1b) is chemically related to milbemycins which is derived from the fermentation product nemadectin [3]. Moxidectin is much more lipophilic in nature than ivermectin and is mainly stored in fat tissues. This could be the explanation for the accumulation effect and for the longer mean residence time for the drug in the body as has been demonstrated in cattle [4].

Both ivermectin and moxidectin have excellent broad spectrum antiparasitic activity against nematodes and arthropods in domestic animals.

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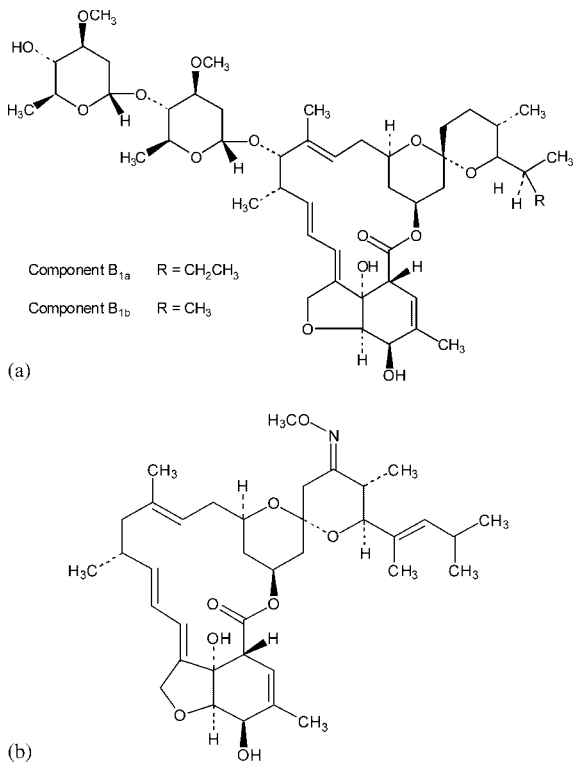

Figure 1. Chemical structures of (a) ivermectin and (b) moxidectin

They exhibit endectocide activity at an extremely low dosage rate [5]. In dogs it has been shown that both ivermectin [6] and moxidectin [7] can be used as a prophylactic treatment for heartworm, *D. immitis*. Both drugs exert excellent activity against many canine nematodes and against several ectoparasites. Ivermectin has shown to have high activity against fourth stage larvae and microfilaria with no activity against adult *D. immitis* [2]. Ivermectin was the first in this family of drugs to be approved for use in preventing heartworm infection and is now marketed for use as a monthly prophylactic. Moxidectin has recently been developed for use in dogs. Efficacy and safety of moxidectin in prevention of adult heartworm infection in dogs has been confirmed [8].

Disposition kinetics of both ivermectin and moxidectin have been reported in the literature for many different animal species. In contrast there is limited information about the pharmacokinetic behavior of these drugs in dogs. The pharmacokinetic behavior of moxidectin has been recently described after oral administration in dogs [9]; however, no reference was found in the literature describing the comparative disposition kinetics of ivermectin and moxidectin in this species. As the pharmacokinetic behavior of anthelmintic drugs can be influenced by many factors such as the route of administration, formulation and animal species [10], the characterization of specific disposition kinetic variables in different animal species is crucial for the appropriate therapeutic use of these agents.

The purpose of this study was to evaluate the comparative pharmacokinetics of ivermectin and moxidectin in dogs after oral administration.

Materials and Methods

Materials

Moxidectin (Lot AC10731-88C) was obtained from Analytical Standards Distribution, America Cyanamid, Princeton, NJ, USA and ivermectin (Lot 56H0254) was purchased from Sigma (St Louis, MO, USA). Trifluoroacetic acid anhydride and *N*-methylimidazole of analytical grade were purchased from Aldrich and Sigma (St Louis, MO, USA), respectively. Acetonitrile, methanol and tetrahydrofluran (HPLC grade) were obtained from Fisher Scientific (New Jersey, USA). The high-performance liquid chromatograph consisted of a Model 501 Solvent Delivery System (Waters, Milford, MA), WISP model 7108 automatic injector (Waters, Milford, MA), a model RF551 fluorescence detector (Shimadzu, Kyoto, Japan) and a chromatopac model CR501 computing integrator (Shimadzu, Kyoto, Japan).

Animals and data collection

Beagle dogs were infected by subcutaneous injection with 200 infective larvae of *Brugia pahangi*, 100 larvae in each hind paw, 144 days before treatment. Sixteen microfilaremic beagles (9 females and 7 males) weighing between 7.9 and 16.3 kg were used in this trial. The animals were selected randomly and allocated into two groups of eight animals each. Animals in each group received either ivermectin or moxidectin

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by oral route at a dose of 250 μg/kg. All the oral doses of moxidectin and ivermectin were given by gavage with commercial injectable formulations of moxidectin (Cydectin® 1% Soluzione Inettabile per Bovini, Cyanamid Italia S.p.A., Rome, Italy) and ivermectin (Ivomec 1% injection for cattle and swine, Merial). Blood samples were collected from each animal at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 12, 24, 72, 120, 168, 240, 336, 432, 528, 624, 1344 h after drug administration. All plasma samples were separated by centrifugation and stored frozen at −80°C until analysis. Furthermore, the dogs were bled for microfilarial counts to study the efficacy of moxidectin and ivermectin in beagles. The maintenance and care of the laboratory animals complied with the guidelines set out in the guide for the Care and Use of Laboratory Animals (National Institutes of Health, Bethesda, MD).

Analytical method

Moxidectin and ivermectin were analysed by high performance liquid chromatography (HPLC), according to the methods previously described for ivermectin [11] and moxidectin [12]. Acetonitrile (100 μl) and water (40 μl) were added to 200 μl of plasma. After mixing for 30 s, the samples were centrifuged at $2500 \times g$ for 10 min, and the supernatant applied to an extraction cartridge (Waters Oasis, HLB cartridge, 30 mg, 1 ml) pretreated with 1 ml methanol, followed by 1 ml of water. The cartridge was washed with 2 ml of water, followed by 2 ml of 25% methanol (vacuum set at 5 mmHg). Ivermectin or moxidectin were eluted with 2 ml of isopropanol (vacuum set at 4 mmHg) and concentrated to dryness under a stream of nitrogen at 50°C in a water bath. The dried residue was dissolved in 100 μl of the *N*-methylimidazole solution in acetonitrile. To initiate the derivatization, 150 μl of trifluoroacetic anhydride solution in acetonitrile was added. After mixing well, an aliquot (100 μl) of this solution was injected directly into the chromatographic system. The mobile phase was a mixture of THF, acetonitrile and water (40:40:20) % v/v at a flow rate of 1 ml/min. An Ultrasphere C_{18} (Beckman Coulter, Fullerton, CA) analytical column was used. Ivermectin and moxidectin were detected with a fluorescence detector with an excitation wavelength of 365 nm and an emission wavelength of 475 nm. Satisfactory linearity and precision (less than 15% coefficient of variation) was achieved for both compounds. The limit of quantitation was 0.2 ng/ml for both ivermectin and moxidectin.

Data analysis

The plasma concentration vs time profiles after each treatment in each individual animal were analysed using a two-compartment open model (first-order input with lag time), with the non-linear regression program WinNonlin v. 4.1 [13]. The Gauss–Newton algorithm of WinNonlin was used for non-linear estimation with a weighting factor of 1/ (observed concentration). Data were also analysed using a non-compartmental approach. The Akaike Information Criterion (AIC), coefficient of determination, coefficient of variation and visual inspection of plots were used to select the best model to define the plasma concentration-time data for each animal. The terminal (elimination) half-life ($T_{1/2\beta}$), distribution half-life ($T_{1/2\alpha}$) and absorption half-life ($T_{1/2ka}$) were calculated as $\ln 2/\beta$, $\ln 2/\alpha$ and $\ln 2/ka$, respectively. The time to reach peak concentration (T_{max}) and peak concentration (C_{max}) were read from the plotted concentration-time curve of each drug in each individual animal. The area under the plasma concentration versus time curve (*AUC*) and the mean residence time (*MRT*) were calculated by the trapezoidal rule with extrapolation to infinity by dividing the last experimental concentration by the terminal slope. The pharmacokinetic parameters are reported as mean ± SD and were statistically compared by the Student's *t*-test. Mean values were considered significantly different at $p < 0.05$.

Results

Eight beagle dogs (4 males and 4 females) with weight ranging from 7.9 to 16.3 kg (mean ± S.D.: 11.2 ± 2.5 kg) received an oral dose of 250 μg/kg of oral ivermectin. Eight additional dogs (3 males and 5 females) with weights ranging from 9.1 to 15.1 kg (mean ± SD: 12.2 ± 1.8 kg) received an oral dose of 250 μg/kg moxidectin. The mean

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plasma concentrations of both drugs after oral administration of 250 μg/kg dog body weight were compared in Figure 2. Parent drug was detected in plasma for 26 days post-treatment for ivermectin and 56 days post-treatment for moxidectin. No clinical signs of drug intolerance were noticed during the period of observation after administration of ivermectin and moxidectin.

Table 1 summarizes the mean pharmacokinetic parameters for ivermectin and moxidectin obtained after oral administration to dogs according to the non-compartmental method. With this analysis both drugs showed a similar pattern of absorption. Higher values of peak plasma concentrations (C_{max}) were obtained for moxidectin (234.0 ± 64.3 ng/ml) compared with ivermectin (132.6 ± 43.0 ng/ml). The terminal elimination half-life was significantly longer in the moxidectin-treated group (621.3 ± 149.3 h) than for the group treated with ivermectin (80.3 ± 29.8 h, $p < 0.01$). Moreover, the value for the mean residence time was significantly longer in the moxidectin-treated group (696.6 ± 188.9 h) than for the group treated with ivermectin (98.4 ± 25.6 h, $p < 0.01$). Since intravenous data are not available for ivermectin and moxidectin, the V_{ss} and CL represent their true values divided by the bioavailability (F) and are expressed as either V_{ss}/F or CL/F. Moxidectin had a lower clearance (0.0220 ± 0.00381 l/h/kg) than ivermectin (0.0498 ± 0.01791/h/kg, $p < 0.01$). The volume of distribution for moxidectin (19.21 ± 3.611/kg) was statistically different from ivermectin (5.35 ± 1.291/kg, $p < 0.01$). In

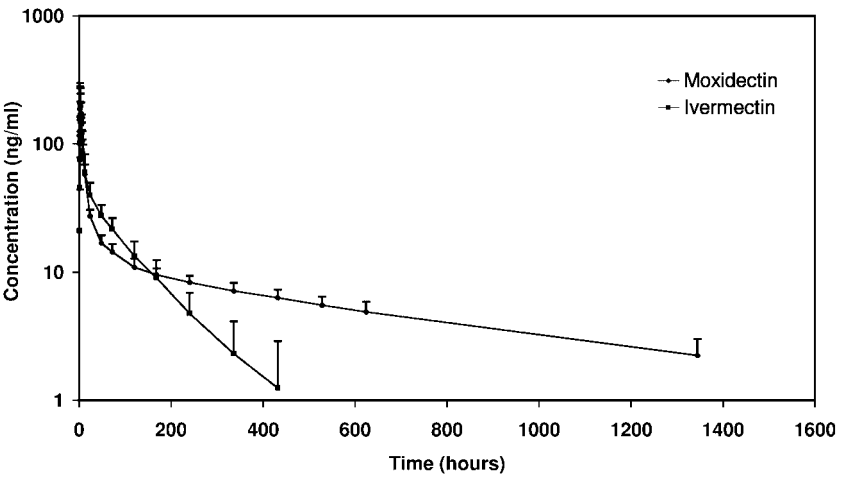

Figure 2. Mean plasma concentrations (ng/ml) for moxidectin (0.25 mg/kg) and ivermectin (0.25 mg/kg) after oral administration in dogs. Each point represents the mean ± SD ($n = 8$)

Table 1. Pharmacokinetic parameters (mean ± SD) of ivermectin and moxidectin in the plasma of dogs following oral administration according to non-compartmental analysis

Parameter	Ivermectin ($n = 8$)	Moxidectin ($n = 8$)	p
C_{max} (ng/ml)	132.6 ± 43.0	234.0 ± 64.3	<0.01
T_{max} (h)	4.12 ± 1.43	2.0 ± 1.0	<0.01
AUC_{total} (μg h/ml)	5.6 ± 1.8	11.8 ± 2.3	<0.01
MRT (h)	98.4 ± 25.6	696.6 ± 188.9	<0.01
V_{ss}/F (l/kg)	5.35 ± 1.29	19.21 ± 3.61	<0.01
CL/F (l/h/kg)	0.0498 ± 0.0179	0.0220 ± 0.00381	<0.01
$T_{1/2\beta}$ (h)	80.3 ± 29.8	621.3 ± 149.3	<0.01

C_{max}, peak plasma concentration; T_{max}, time to peak plasma concentration; AUC_{total}, area under the concentration-time curve extrapolated to infinity; *MRT*, mean residence time; V_{ss}/F, volume of distribution at steady-state; CL/F, total body clearance; V_{ss} and CL represent their true values divided by the systemic availability (F); $T_{1/2\beta}$, terminal elimination half-life.

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comparison with ivermectin, no satisfactory fit was obtained with the two-compartmental model; therefore the moxidectin pharmacokinetic behavior was only described by the non-compartmental method. A three-exponential equation corresponding to a two-compartmental model with a lag time and first order absorption was the best model to describe the pharmacokinetic data of ivermectin. In the compartmental analysis (Table 2), the kinetic parameters for ivermectin are consistent with those of the non-compartmental method. Similar C_{max}, T_{max}, AUC, V_{ss}, CL/F and $T_{1/2\beta}$ were obtained with both models. The mean estimates of absorption rate constant (K_a) and distribution half-life ($T_{1/2\alpha}$) for ivermectin were ($0.683 \pm 0.283\,h^{-1}$) and (3.16 ± 1.07 h), respectively. There was no statistically significant sex difference in any of the fundamental pharmacokinetic parameters in ivermectin and moxidectin treated groups. For ivermectin, the volume of distribution was higher in males (6.15 ± 1.20 l/kg) compared with female dogs (4.55 ± 0.86 l/kg). Also a trend was observed for lower clearance of ivermectin in females (0.0417 ± 0.0127 l/h/kg) compared with male dogs (0.0578 ± 0.0203 l/h/kg). In the moxidectin treated group, the volume of distribution was slightly higher in female (20.25 ± 3.11 l/kg) compared with male dogs (17.49 ± 4.37 l/kg). The $T_{1/2\beta}$ for moxidectin in female dogs (678.8 ± 145.0 h) was slightly higher than in males (525.4 ± 118.1 h).

Table 2. Pharmacokinetic parameters (mean ± SD) of ivermectin in the plasma of dogs following oral administration according to compartmental analysis ($n = 8$)

Parameter	Mean (± SD)
A (ng/ml)	439 ± 462
α (h^{-1})	0.242 ± 0.081
B (ng/ml)	42.9 ± 9.4
β (h^{-1})	0.00942 ± 0.002
K_a (h^{-1})	0.683 ± 0.283
$T_{1/2ka}$ (h)	1.2 ± 0.54
C_{max} (ng/ml)	122.6 ± 38.6
T_{max} (h)	3.65 ± 1.18
AUC_{total} (μg h/ml)	5.4 ± 1.7
V_1/F (l/kg)	1.35 ± 0.41
V_2/F (l/kg)	3.44 ± 1.08
V_{ss} (l/kg)	4.79 ± 0.49
CL/F (l/h/kg)	0.0519 ± 0.0193
$T_{1/2\alpha}$ (h)	3.16 ± 1.07
$T_{1/2\beta}$ (h)	76.0 ± 16.3

A, distribution phase intercept; α, distribution rate constant; B, elimination phase intercept, β, elimination rate constant; K_a, absorption rate constant; $T_{1/2ka}$, time of half-life of absorption; C_{max}, peak plasma concentration; T_{max}, time to peak plasma concentration; AUC_{total}, area under the concentration-time curve extrapolated to infinity; V_1/F: volume of distribution of central compartment; V_2/F, volume of distribution of peripheral compartment; V_{ss}/F, volume of distribution at steady-state; CL/F, total body clearance; V_1, V_2, V_{ss} and CL represent their true values divided by the systemic availability (F); $T_{1/2\alpha}$ and $T_{1/2\beta}$, time of half-lives of distribution and terminal phases respectively.

Discussion

The purpose of this study was to evaluate the comparative disposition plasma kinetic profiles for ivermectin and moxidectin after oral administration to beagle dogs. Ivermectin is the most extensively studied of the macrocyclic agents; its disposition kinetics was studied in sheep [14,15], cattle [4,16], horses [17], pigs [18], goats [19] and camels [20]. The plasma disposition kinetics of moxidectin has been studied in sheep [21], cattle [4], horses [17], goats [22] and camels [20]. Tables 3 and 4 summarize the available fundamental

Table 3. Fundamental pharmacokinetic parameters of ivermectin in various species and humans

	CL/F (l/h/kg)	V_{ss}/F (l/kg)	$T_{1/2\beta}$ (day)	Reference
Sheep			3.7	14
Cattle	0.019	3.4	4.3	4, 16
Horses			4.3	17
Dogs	0.0498	5.4	3.3	This study
Pigs			3.8	18
Goats			4	19
Humans			0.5	27

Table 4. Fundamental pharmacokinetic parameters of moxidectin in various species and humans

	CL/F (l/h/kg)	V_{ss}/F (l/kg)	$T_{1/2\beta}$ (day)	Reference
Sheep			21	21
Cattle	0.0391	13.6	14.5	4
Horses			23.1	17
Dogs	0.0220	19.2	25.9	This study
Goats			12	22
Humans			20.2–35.1	28

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pharmacokinetic parameters (CL, V_{ss}, and $T_{1/2\beta}$) in various species and humans for ivermectin and moxidectin, respectively. The dose selection in our study was based on doses used in preclinical efficacy testing and potential therapeutic dose levels in humans.

The two-compartment model was applied in the pharmacokinetic analysis of the data for both drugs. For ivermectin, excellent criteria of fit were obtained with respect to random scatter in the residual plots and excellent precision of the model parameters. For moxidectin, with the rapid absorption and pronounced distribution phases, there was difficulty in obtaining unbiased residuals of the peak concentrations and precise estimation of the pharmacokinetic parameters using the two-compartment model. Therefore, we chose to report the pharmacokinetic data for these drugs using the results from non-compartmental modeling.

The drugs were administered as oral solutions and no significant lag time was found for absorption. It was found that the absorption of both ivermectin and moxidectin was rapid after oral administration. Maximum plasma concentrations of moxidectin were attained earlier and to a greater extent than ivermectin. These findings indicate a slightly faster absorption rate of moxidectin compared with ivermectin. A T_{max} of around 4 h was found by Daurio *et al.* following oral administration of ivermectin to dogs which is similar to the T_{max} obtained in the current trial [6]. An earlier T_{max} of ivermectin was obtained in this study compared with oral administration of the same drug in sheep [23]. This faster absorption rate is expected in non-ruminant species. In sheep [14] a T_{max} of 16.4 h was reported for ivermectin after oral administration compared with a value of 5.3 h for moxidectin [21] obtained using the same route and dose indicating a more rapid absorption of moxidectin in this species. Our results are also in agreement with those reported in cattle [4]. When the same dose of both drugs was administered subcutaneously in steers, moxidectin had a more rapid of absorption and earlier T_{max} than ivermectin.

Since ivermectin and moxidectin are highly lipophilic and difficult to administer by the intravenous route, the absolute bioavailability of these drugs after oral administration has not yet been documented. However, bioavailability relative to the subcutaneous route has been calculated in some species. In horses and sheep bioavailability was found to be approximately 36% [14]. A relative systemic bioavailability of 27% was found for moxidectin in goats [22]. It appears that ruminants only absorb 1/4–1/3 of a dose of ivermectin and moxidectin. The bioavailability of these drugs is greater after subcutaneous administration, but absorption after oral dosing is more rapid than after subcutaneous [2].

Ivermectin and moxidectin are highly lipophilic drugs with extensive distribution to various tissues. A significantly ($p < 0.01$) larger V_{ss}/F was obtained for moxidectin (19.21 ± 3.61 l/kg) compared with ivermectin (5.35 ± 1.29 l/kg). The extensive tissue distribution of these drugs in dogs agrees with the volume of distribution values obtained in our trial. The volume of distribution of moxidectin in the current trial is similar to the value reported by Vanapalli *et al.* after oral administration of the same drug in dogs [9]. In cattle a large volume of distribution of 13.6 l/kg was obtained for moxidectin, while values of 3.4 l/kg were found for ivermectin when both drugs were given subcutaneously at the same dose [4]. In sheep a volume of distribution (5.3 l/kg) was reported after intravenous administration of ivermectin [15].

The total body clearance for ivermectin and moxidectin was low. Moxidectin had lower clearance (0.0220 ± 0.00381 l/h/kg) than ivermectin (0.0498 ± 0.0179 l/h/kg, $p < 0.01$). The clearance in the current trial for moxidectin is similar to the value reported by Vanapalli *et al.* (0.0237 l/h/kg) after oral administration of the same drug in dogs [9]. Ivermectin and moxidectin total clearance appears to be low in most species. In cattle, the total clearance of ivermectin and moxidectin was 0.0190 l/h/kg and 0.0391 l/h/kg, respectively, after subcutaneous administration [4]. The pharmacokinetics behavior of ivermectin and moxidectin are characterized by a long persistence in the body due to a low plasma clearance and to an extensive distribution into fat consistent with the physiochemical prosperities of these drugs.

The terminal elimination half-life for ivermectin was 3.3 days, a value which differs from that

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reported by Lo and coworkers of 1.8 days [24] and Kojima *et al.* (1.4 days) [25] after administration of the drug in dogs. In the moxidectin treated group of dogs the elimination half-life was 25.9 days, a value that is higher than that reported by Vanapalli *et al.* of 19.1 days after oral administration of the same drug in this species [9]. Our results of a longer elimination half-life for ivermectin and moxidectin compared with previous studies can be attributed to the longer sampling period in this trial. To accurately determine half-life it is desirable to sample over a period of two elimination half-lives, which was done in this study. On a comparative basis the elimination half-life of moxidectin is about eight-fold longer than that of ivermectin. The longer mean residence time for ivermectin and moxidectin are related to the relatively low plasma clearances and high volumes of distribution of these agents. The mean residence time for moxidectin was about seven-fold longer than ivermectin. Our results agree with the elimination half-life obtained in horses after oral administration of ivermectin (4.3 days) and moxidectin (23.1 days) [17]. The half-life of ivermectin in our study was similar to those obtained after subcutaneous administration of the same drug in sheep [14], cattle [16] and pigs [18].

The findings related to sex analysis obtained in this study for the moxidectin treated group were similar to those previously reported by Vanapalli *et al.* after oral administration of moxidectin to dogs. Vanapalli *et al.* found that female dogs have longer elimination half-lives compared with male dogs (statistically significant for 250 μg/kg dose). He also observed a trend of increased volume of distribution in female dogs compared with male dogs [9]. A trend was observed which did not reach statistical significance (with a smaller number of animals), of increased volume of distribution and terminal elimination half-life in the female moxidectin treatment group compared with the male treatment group.

A strong relationship between disposition kinetics and clinical efficacy for antiparasitic drugs has been documented. Antiparasitic activity not only depends on the interaction between drug and its target receptor, but also on the presence of a high concentration of the drug at the site of action [26]. Characterization and evaluation of comparative pharmacokinetics profiles can be used to optimize drug efficacy. In conclusion, ivermectin pharmacokinetics was described using a two-compartmental model and ivermectin and moxidectin were described using non-compartmental methods. In dogs, ivermectin and moxidectin showed a rapid absorption with a pronounced phase of distribution. Oral administration of moxidectin produced higher plasma concentrations than ivermectin and resulted in a more prolonged residence in the dogs. Compared with ivermectin, moxidectin has a lower clearance and higher volume of distribution which results in a prolonged elimination half-life. The results in this study contribute to further understanding of the plasma disposition kinetics of ivermectin and moxidectin in dogs.

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