Bioavailability of a commercial formulation of ivermectin after subcutaneous administration to sheep

Aranzazu Gonzalez Canga, PhD; Ana Sahagun, PhD; M. Jose Diez, PhD; Nelida Fernandez, PhD; Matilde Sierra, PhD; Juan J. Garcia, PhD

Objective—To evaluate bioavailability and other pharmacokinetic variables of a commercial formulation of ivermectin after IV administration to sheep.

Animals—6 healthy adult sheep.

Procedures—A single dose of a commercial formulation of ivermectin (200 µg/kg) was administered IV to each sheep. After a washout period of 3 weeks, each sheep was administered ivermectin by SC injection. Plasma samples were obtained for up to 36 and up to 42 days after IV and SC administration, respectively. Ivermectin concentrations were quantified by use of high-performance liquid chromatography with fluorescence detection.

Results—Results obtained indicated that after IV administration, ivermectin is cleared slowly from plasma, tends to distribute and accumulate in the peripheral compartment, and is slowly eliminated from the body. After SC administration, noncompartmental analysis revealed that bioavailability of ivermectin is nearly complete (98.20%), has a slow mean absorption time of 0.96 days, and reaches a maximum plasma concentration of 19.55 ng/mL at 3.13 days.

Conclusions and Clinical Relevance—The commercial formulation of ivermectin used in this study can be administered SC to sheep on the basis of a nearly complete bioavailability. In addition, the maximum plasma concentration and interval from SC injection until maximum plasma concentration is obtained are higher than those reported by other authors who used other routes of administration. (*Am J Vet Res* 2007;68:101–106)

Ivermectin, a semisynthetic derivative of avermectin B_1 produced by the soil-dwelling actinomycete *Streptomyces avermitilis*, is a highly effective parasiticide that belongs to the macrocyclic lactone class of compounds.[1] The drug was introduced on the market in 1981, and since then, it has found wide use as an antiparasitic agent against endoparasites and ectoparasites of animals, including cattle, sheep, swine, horses, and dogs. It is also used as an extremely effective treatment for humans with filarial worm infections.[2,3,a]

Anthelmintic activity relates to the action of a drug on parasites and the effective concentrations of the drug and its metabolites at the site of action. The use of a pharmacokinetic evaluation for assessing the efficacy of an anthelmintic assumes that the plasma concentration pattern of the anthelmintic, its active metabolites, or both is related to the concentration of the active moiety at the site of action.[4] Therefore, adequate knowledge of the pharmacokinetic characteristics of the macrocyclic lactone endectocides, and of ivermectin in particular, could be important for the design of programs for the control of gastrointestinal nematodes and lung worms.[5]

Abbreviations

HPLC	High-performance liquid chromatography
λ	Plasma elimination rate constant
AUC	Area under the plasma concentration–time curve
AUMC	Area under the first moment curve
$t_{1/2\lambda}$	Half-life associated with the λ phase
MRT	Mean residence time
MAT	Mean absorption time
Cl	Total body clearance
Vd_{ss}	Volume of distribution at steady state
Vd_a	Apparent volume of distribution
C_{max}	Maximum plasma ivermectin concentration
t_{max}	Time to reach C_{max}
$t_{1/2\alpha}$	Half-life associated with the α phase
$t_{1/2\beta}$	Half-life associated with the β phase
Vd_c	Apparent volume of distribution for the central compartment
$t_{1/2k10}$	Half-life for elimination from the central compartment

Although the pharmacokinetic behavior of ivermectin has been widely studied in sheep,[6-19] reports on the pharmacokinetic variables are scarce. On the other hand, it has been reported[20] that the pharmacokinetic variables of ivermectin differ on the basis of the formulation used, route of administration, and animal species. The vehicle in which compounds are formulated may play a relevant role in their absorption kinetics and

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From the Department of Pharmacology and Toxicology, Veterinary Faculty, University of León, Campus de Vegazana s/n 24071, León, Spain.
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Address correspondence to Dr. Gonzalez Canga.

plasma availability.[6,21] Thus, small differences in formulation can alter disposition kinetics and may result in important changes in activity against endoparasites and ectoparasites in livestock.

The objective of the study reported here was to evaluate pharmacokinetics of a commercial formulation of ivermectin after SC administration to sheep. The SC route of administration is recommended for this formulation. Ivermectin was also administered IV to the same sheep to establish the elimination kinetics and bioavailability of this compound.

Materials and Methods

Animals—Six healthy nonlactating adult female Merino sheep (age, 4 years; range of body weight, 43.5 to 65.0 kg) were used in the study. Health of the sheep was closely monitored before and throughout the study. Protocols and procedures for this experiment were approved by the Institutional Animal Care and Use Committee of the University of León.

Sheep were housed indoors in an adequately ventilated building. Sheep were fed lucerne hay mixed with straw and concentrate each day; fresh water was available ad libitum. Sheep were housed in these conditions for 2 weeks before drug administration to allow adaptation to the environment and to prevent stressful situations during the experiment.

Study design—Each sheep was initially administered a single dose of ivermectin[b] (200 µg/kg, IV) in the left jugular vein. Ivermectin was dissolved in a mixture of propylene glycol[c]:glycerol formal[d] (60:40 [vol:vol]) containing 5% polyvinylpyrrolidone.[e] Blood samples (5 mL) were collected from a jugular vein (alternating between left and right) into heparinized vacuum tubes.[f] Samples were obtained before administration (time 0) and 2, 4, 7, 10, 15, 21, 33, 45, and 57 hours and 3, 4, 5, 6, 8, 10, 14, 18, 24, 30, and 36 days after IV administration.

After a washout period of 3 weeks that began after the last blood sample was collected on day 36 after IV administration, the same sheep were administered a single dose of a commercial formulation of ivermectin[g] (200 µg/kg, SC). This dose was selected because it was the dose recommended by the manufacturer. Injections were administered in the shoulder area. Blood samples (5 mL) were obtained from both jugular veins (alternating between left and right) before administration (time 0) and 6, 12, 24, 36, 42, 48, 54, 60, and 66 hours and 3, 4, 5, 6, 8, 10, 14, 18, 24, 30, 36, and 42 days after SC administration.

All blood samples were handled in a similar manner. Plasma was immediately separated by use of centrifugation (3,000 × g for 20 minutes), harvested, and stored frozen in polypropylene vials at –80°C until analyzed. All samples were analyzed within 60 days after they were obtained.

Analytical procedures—Ivermectin was assayed by use of HPLC with liquid-phase extraction and fluorescence detection, in accordance with a validated method.[22] Ivermectin was extracted from spiked and unknown plasma samples. Briefly, 100 µL of plasma and 16 µL of internal standard (doramectin[h]) in a solution of 0.1 µg of dimethylsulfoxide/mL of water were added to a 1.5-mL tube. The mixture was vortexed vigorously for 30 seconds, and 500 µL of chilled (–30°C) methanol was added. Extraction was performed by shaking the reaction tube for 30 seconds, which was followed by incubation at –30°C for 10 minutes. The tube was then centrifuged (16,000 × g for 12 minutes at 4°C), and the upper phase was transferred to another tube, evaporated in a water bath (50°C), and dried under a gentle stream of nitrogen gas. The dried residue was resuspended in 100 µL of a mixture of N-methylimidazole:acetonitrile (1:1 [vol:vol]). Subsequently, 150 µL of a mixture of trifluoroacetic anhydride:acetonitrile (1:2 [vol:vol]) was added as a derivative. After incubation for < 30 seconds, 2 aliquots (100 µL/aliquot) were injected into the chromatograph.

The mobile phase consisted of a mixture of methanol[i]:acetonitrile[j]:0.2% acetic acid[k] in water (45:50:5 [vol:vol:vol]) at a flow rate of 2 mL/min. The mobile-phase solvents were all HPLC-grade quality. Fluorescence detection was performed at 365 nm (excitation) and 475 nm (emission).

Analyses were performed on an HPLC system[l] equipped with a scanning fluorescence detector[m] by use of a C18 reverse-phase column[n] (140 × 3.9 mm; 5-µm particle size). Acquisition of chromatography data was performed by use of a software package.[o]

Interday and intraday accuracy and precision were within 10%. The quantification and detection limits of the method (0.1747 and 0.0629 ng/mL, respectively) were determined in accordance with an equation described elsewhere.[22] Mean ± SD extraction recovery from plasma was 86.50 ± 5.12% for plasma samples spiked with concentrations ranging from 0.25 to 100 ng/mL.

Pharmacokinetic analysis—Pharmacokinetic analysis was performed on the basis of compartmental and noncompartmental descriptions of the observed data. For compartmental analysis, plasma ivermectin concentration–time patterns were individually fitted to the following exponential equation:

$$C_p = \sum_{i=1}^{n} C_i e^{-\lambda_i t}$$

where C_p is the plasma concentration of ivermectin, n is the number of exponential terms, C_i is the y-intercept, e is the exponential function (base e), λ_i is the slope of each n first-order rate process, and t is time. Data were fitted to the equation by use of a weighting factor ($1/C^2$), where C is the ivermectin concentration. The pharmacokinetic model best describing the plasma ivermectin concentration–time curves was determined by use of a computer program.[p]

The best fit was determined on the basis of Akaike information criterion[23] and graphic analysis of weighted residuals. Other compartmental variables were calculated by the use of standard methods.[24,25]

The same computer program[p] was used for the noncompartmental analysis. The value for λ was deter-

mined by use of least squares regression of the logarithm of plasma concentration–versus–time curve for the terminal elimination phase. Values for AUC and AUMC were calculated by the linear trapezoidal rule with extrapolation to infinity. The $t_{1/2\lambda}$ was calculated as the quotient of $0.693/\lambda$. The Cl was calculated as dose/AUC. The MRT was calculated as AUMC/AUC, and MAT was defined as $MRT_{SC} - MRT_{IV}$, where MRT_{SC} and MRT_{IV} were the MRT after SC and IV administration, respectively. The Vd_{ss} was calculated as MRT × (dose/AUC), and the Vd_a was calculated as Cl/λ. Values for C_{max} and t_{max} were determined by direct observation of the data. The subcutaneously absorbed fraction (ie, bioavailability) was calculated as $(AUC_{SC}/AUC_{IV}) \times 100$, where AUC_{SC} and AUC_{IV} were the AUC values after SC and IV administration, respectively.

Statistical analysis—All pharmacokinetic variables were calculated for each sheep. Values for each sheep were used to calculate the mean ± SD. Data were analyzed by use of the skewness test (to determine normality) and Cochran test (to determine uniformity in the variance). When the data were normally distributed and there was uniformity in the variance, a *t* test was used to evaluate differences between data sets. When the data were not normally distributed or there was not uniformity in the variance, a Wilcoxon test was used. Values of $P \leq 0.05$ were considered significant for all analyses. A statistical computer program[q] was used for all statistical analyses.

Results

All sheep tolerated well the IV or SC administration of ivermectin. No adverse effects were observed in any of the sheep.

Mean plasma ivermectin concentration as a function of time after IV and SC administration of a single dose of ivermectin (200 µg/kg) was plotted (**Figure 1**). Pharmacokinetics of ivermectin were best described by a 2-compartment open model after IV administration and by a 1-compartment open model with first-order absorption after SC administration. However, the precision of estimates obtained by compartmental analysis for several variables after SC administration was not sufficient, so we considered the noncompartmental analysis to be the best option for use in evaluating kinetics of ivermectin after SC administration.

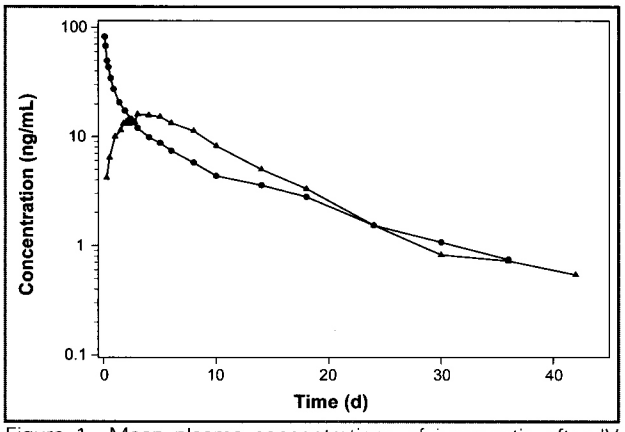

Figure 1—Mean plasma concentrations of ivermectin after IV (circles) and SC (triangles) administration of a single dose (200 µg/kg) to 6 sheep.

Compartmental analysis after IV administration revealed that ivermectin disappeared slowly from plasma, with mean values for $t_{1/2\alpha}$ and $t_{1/2\beta}$ of 0.728 and 9.598 days, respectively (**Table 1**). Ivermectin tends to distribute and accumulate in the peripheral compartment, as verified by values for the apparent first-order transfer rate constant from the central compartment to the peripheral compartment and apparent first-order transfer rate constant from the peripheral compartment to the central compartment and from the fact that the value for the apparent volume of distribution for the peripheral compartment (8.01 L/kg) was higher than the value for Vd_c (3.01 L/kg). Finally, the value obtained for Cl (1.166 L/kg/d) indicated that the drug was slowly eliminated from the body.

Main noncompartmental pharmacokinetic variables determined after IV administration were MRT (10.30 days), AUC (197.03 ng × [d/mL]), and Cl (1.114 L/kg/d; **Table 2**). Significant differences were found between values for AUC and total body clearance obtained by compartmental and noncompartmental methods. After SC administration of the commercial formulation, noncompartmental analysis revealed that ivermectin was absorbed slowly from the site of injection and reached

Table 1—Mean ± SD and range values for pharmacokinetic variables obtained by use of compartmental analysis after IV administration of a single dose of ivermectin (200 µg/kg) to 6 sheep.

Variable	Mean ± SD	Range
A (ng/mL)	59.72 ± 13.20	42.68–75.58
B (ng/mL)	10.32 ± 5.81	5.80–21.30
α (/d)	1.254 ± 0.481	0.364–1.744
β (/d)	0.077 ± 0.024	0.057–0.115
AUC (ng × [d/mL])	189.83 ± 56.20	96.40–229.54
Cl (L/kg/d)	1.166 ± 0.473	0.796–2.075
Vd_c (L/kg)	3.01 ± 0.75	2.14–4.12
Vd_{ss} (L/kg)	11.02 ± 3.24	6.17–14.89
Vd_a (L/kg)	15.54 ± 4.80	7.55–21.23
$T_{1/2\alpha}$ (d)	0.728 ± 0.579	0.397–1.903
$T_{1/2\beta}$ (d)	9.598 ± 2.490	6.005–12.143
C_0 (ng/mL)	70.04 ± 17.45	56.42–93.47

A = Zero-time intercept for the α phase. B = Zero-time intercept for the β phase. α and β are apparent first-order disposition rate constants for the α and β phase, respectively. C_0 = Addition of the α and β zero-time intercepts.

Table 2—Mean ± SD and range values for pharmacokinetic variables obtained by use of noncompartmental analysis after IV administration of a single dose of ivermectin (200 µg/kg) to 6 sheep.

Variable	Mean ± SD	Range
λ (/d)	0.072 ± 0.036	0.048–0.144
AUC (ng × [d/mL])*	197.03 ± 57.16	104.56–259.77
AUMC (ng × [d^2/mL])	2,083.9 ± 938.27	53.1–3,632.5
MRT (d)	10.30 ± 2.71	7.19–13.98
Cl (L/kg/d)*	1.114 ± 0.424	0.770–1.913
Vd_{ss} (L/kg)	11.01 ± 3.16	6.09–14.35
Vd_a (L/kg)	17.61 ± 7.93	5.89–30.67
$t_{1/2\lambda}$ (d)*	10.982 ± 3.447	4.823–14.507

*Value differs significantly ($P < 0.05$) with value for the same variable in the corresponding compartmental analysis.

Table 3—Mean ± SD and range values for pharmacokinetic variables obtained by use of noncompartmental analysis after SC administration of a single dose of ivermectin (200 µg/kg) to 6 sheep.

Variable	Mean ± SD	Range
λ (/d)	0.148 ± 0.075	0.062–0.283
AUC (ng × [d/mL])	190.74 ± 59.74	119.43–280.50
AUMC (ng × [d²/mL])*	1,860.1 ± 840.6	695.3–3,177.5
MRT (d)	9.41 ± 2.07	5.82–11.33
MAT_{0-t} (d)	0.96 ± 0.56	0.22–1.56
Cl/F (L/kg/d)	1.135 ± 0.345	0.713–1.675
Vd_a/F (L/kg)	8.36 ± 1.88	5.93–11.53
$t_{1/2\lambda}$ (d)*	5.771 ± 2.981	2.454–11.207
C_{max} (ng/mL)	19.55 ± 5.03	12.88–25.54
t_{max} (d)	3.13 ± 1.22	1.75–5.00
F (%)	98.20 ± 16.08	72.34–114.23

*Value differs significantly ($P < 0.05$) from the value for the same variable for IV administration in the corresponding noncompartmental analysis.
MAT_{0-t} = MAT from time 0 to the last sampling time. F = Bioavailability.

a C_{max} of 19.55 ng/mL at 3.13 days (Table 3). Bioavailability after SC administration was 98.20%.

Curves had fewer experimental points after SC administration than after IV administration because plasma concentrations for the last sample collection time points were less than the limit of detection. Because of this fact, we considered the MAT from 0 to infinity (0.96 days) was most representative of the absorption rate.

Variables were determined after IV and SC administration. Analysis revealed that AUMC and $t_{1/2\lambda}$ differed significantly between the routes of administration.

Discussion

Pharmacokinetics of ivermectin after administration to sheep have been widely investigated.[6-19] However, most of those investigations were not a complete study with regard to compartmental and noncompartmental analysis. Some investigators believe that the pharmacokinetic model that best fits the plasma concentrations for ivermectin after IV administration is a 2-compartmental model,[6] whereas others believe the best fit may be a 1-compartmental[16,17] or 2-compartmental[15,26] model after SC administration.

In healthy sheep administered 200 µg of ivermectin/kg, SC, the value of C_{max} calculated by other authors[8-11,15,17,26] ranges from 12 to 35 ng/mL. Results of the study reported here (mean ± SD, 19.55 ± 5.03 ng/mL) are similar to results in another study[15] but are lower than most of the values calculated by other authors.

Pharmacokinetic analysis has been conducted in parasitized sheep. Mean ± SD C_{max} was 35 ± 11 ng/mL in sheep infected with *Nematodirus battus*[11]; 41.21 ± 16.23 ng/mL in sheep infected with *Psoroptes* spp[17]; and 21.7 ± 3.96 ng/mL in lambs infected with *Ostertagia* spp, *Trichostrongylus* spp, and *Cooperia* spp.[19] In comparison to healthy sheep, values obtained for t_{max} were 2.5 days,[8] 2.60 ± 0.55 days,[15] and 2.67 ± 0.52 days.[17] Nevertheless, authors in another study[6] reported that t_{max} is reached before 0.5 days, and other researchers obtained intermediate values (1.5 days,[10] 1.92 ± 0.35 days,[11] 1.24 ± 0.14 days,[26] 1.70 ± 0.65 days [lactating sheep],[16] and 1.75 ± 0.1 days[19]).

In the study reported here, mean ± SD t_{max} was 3.13 ± 1.22 days, and C_{max} was higher than in the aforementioned studies. Values for t_{max} have varied in livestock with various parasitic infections (*N battus*, 1.59 ± 0.72 days[12]; *Psoroptes* spp, 0.90 ± 0.22 days[17]; and lambs infected with *Ostertagia* spp, *Trichostrongylus* spp, and *Cooperia* spp, 1.71 ± 0.01 days[19]).

The value of AUC determined after IV administration of ivermectin (300 µg/kg) in another study[7] was 374.58 ng × (d/mL), which is a value greater than the mean ± SD value determined in the study reported here in which we administered a single dose of 200 µg/kg (compartmental, 189.83 ± 56.20 ng × [d/mL]; noncompartmental, 197.03 ± 57.16 ng × [d/mL]). When a dose of 200 µg/kg was administered SC to healthy sheep in other studies, the value reported for AUC was 238 ng × (d/mL),[8] 281.00 ± 80.80 ng × (d/mL),[15] and 207.47 ± 46.54 ng × (d/mL).[17] However, lower values have been obtained by other researchers (101.67 ± 30.42 ng × [d/mL],[11] 63.99 ± 28.34 ng × [d/mL] in lactating animals,[16] 82.06 ± 50.41 ng × [d/mL],[26] and 134.3 ± 15.7 ng × [d/mL][19]). The value for AUC found after SC administration in the study reported here (190.74 ± 59.74 ng × [d/mL]) is intermediate to values reported by other investigators[11,17] but is considerably higher than the value in another study.[16]

Values of AUC have been determined in sheep with parasitic infections. Mean ± SD AUC in sheep infected with *N battus*[11] was 175.00 ± 38.75 ng × (d/mL), whereas it was 179.96 ± 90.59 ng × (d/mL) in sheep infected with *Psoroptes* spp[17] and 75.2 ± 15.5 ng × (d/mL) in lambs infected with *Ostertagia* spp, *Trichostrongylus* spp, and *Cooperia* spp.[19]

Bioavailability has been determined after SC administration. In another study,[6] investigators indicated that bioavailability after SC administration was 22%, whereas the mean ± SD value for bioavailability in the study reported here was 98.20 ± 16.08%.

The AUMC in healthy sheep administered ivermectin SC in another study[15] was 1,628 ± 138 ng × (d²/mL). The value in that study is similar to the value reported here (1,860 ± 840.6 ng × [d²/mL]) and higher than the value in another study[19] of healthy (496.8 ± 138 ng × [d²/mL]) and parasite-infected (228 ± 58 ng × [d²/mL]) lambs.

Mean ± SD values for MRT after SC administration of ivermectin to healthy sheep in other studies have been high (5.9 ± 0.4 days,[15] 5.2 ± 2.8 days,[16] 8.6 ± 0.7 days,[17] and 3.81 ± 0.29 days[19]). The mean value for MRT determined in the study reported here (9.41 ± 2.07 days) is in concordance with, but slightly higher than, the aforementioned results. In parasitized sheep, investigators obtained an MRT of 6.7 ± 1.9 days in 1 study[17] and 2.93 ± 0.16 days in another study.[19]

Various volumes of distribution have been reported after IV administration of ivermectin to healthy sheep. In 1 study,[6] the value for Vd_c was 4.6 L/kg after administration of a dose of 300 µg/kg, whereas Vd_{ss} was 5.3 L/kg after administration of a smaller dose (200 µg/kg) in another study.[7] The SC administration of ivermectin to lactating sheep yielded a mean ± SD quotient for the volume of distribution divided by bioavailability of 12.8 ± 9.4 L/kg in 1 study,[16] whereas in another study,[17] SC administration yielded a mean Vd_a of 8.8 ± 2.6 L/kg. These high values reflect the wide distribution of ivermectin in the body.

After IV administration in the study reported here, we determined mean ± SD values for Vd_c (3.01 ± 0.75 L/kg), Vd_{ss} (compartmental, 11.02 ± 3.24 L/kg; noncompartmental, 11.01 ± 3.16 L/kg), and Vd_a (compartmental, 15.54 ± 4.80 L/kg; noncompartmental, 17.61 ± 7.93 L/kg). After SC administration, the mean value obtained for Vd_a (8.15 ± 2.20 L/kg) was much lower than the value after IV administration. Similar to results of other authors, the results reported here revealed a large volume of distribution for ivermectin.

In another study,[17] mean ± SD Vd_a in sheep affected with scabies was 6.5 ± 1.7 L/kg. However, the values obtained for Vd_a after SC administration vary (3.7 days,[8] 7.02 ± 2.05 days,[15] 2.85 ± 1.97 days,[16] 5.57 ± 1.25 days,[17] and 1.67 ± 0.40 days[26]).

In the study reported here, mean ± SD values after IV administration were 9.598 ± 2.490 days for $t_{1/2\beta}$ and 1.954 ± 0.705 days for $t_{1/2k10}$. After SC administration, the value for $t_{1/2k10}$ (4.719 ± 0.990 days) was higher and that for $t_{1/2\lambda}$ (5.771 ± 2.981 days) was lower than the value obtained for $t_{1/2\beta}$ after IV administration. The half-life ($t_{1/2\beta}$) reported in sheep infected with *Psoroptes* spp[17] was 5.54 ± 1.44 days.

Mean ± SD value for Cl/bioavailability in healthy lactating sheep that were administered ivermectin SC in another study[16] was 3.238 ± 1.270 L/kg/d. That value is more than twice the value determined for the study reported here (1.135 ± 0.345 L/kg/d).

On the basis of the aforementioned results, it can be deduced that there are large variations among individual animals with regard to the pharmacokinetics of ivermectin. This fact has been reported in cows,[21,27] sheep,[9,11,16] goats,[28] pigs,[29] and deer.[30,31] This has been attributed to several factors, such as differences in breed, age, body weight, body condition, physiologic status, type of feed, or quantity of feed. These factors, as well as others that can influence plasma concentrations of ivermectin (such as route of administration), give rise to differences between our results and results reported by other authors.

In addition, it is important to remember that differences in formulations of ivermectin can be one of the major factors for reported differences. In the study reported here, we evaluated bioavailability and other pharmacokinetic variables for the commercial formulation. For the IV administration, we used a formulation that had the same potency as that for the commercial formulation but that involved another vehicle. Thus, one of the factors that could have affected bioavailability in our study was the vehicle used.

Our findings for noncompartmental analysis after SC administration of a commercial formulation of ivermectin revealed that the bioavailability (98.20%) was characterized by almost total absorption at a slow rate (MAT from time 0 to infinity of 0.96 days). The C_{max} was 19.55 ng/mL, and t_{max} was 3.13 days. On the basis of these results, we conclude that the commercial formulation used in this study is a good option when administering ivermectin to sheep.

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d. Glycerol, Sigma SA, Madrid, Spain.
e. Plasdone C-30, International Specialty Products, Barcelona, Spain.
f. Venoject, Terumo Europe, Leuven, Belgium.
g. Zoomectin, Laboratorios SYVA, León, Spain.
h. Doramectin, Pfizer SA, Madrid, Spain.
i. Methanol, Merck SA, Barcelona, Spain.
j. Acetonitrile, Merck SA, Barcelona, Spain.
k. Acetic acid, Merck SA, Barcelona, Spain.
l. Waters HPLC system, Waters Chromatography SA, Madrid, Spain.
m. Waters 474 scanning fluorescence detector, Waters Chromatography SA, Madrid, Spain.
n. Novapak, Waters Chromatography SA, Madrid, Spain.
o. Empower, Waters Chromatography SA, Madrid, Spain.
p. WinNONLIN, version 4.0.1, Pharsight Corp, Mountain View, Calif.
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