Pharmacokinetics of a novel formulation of ivermectin after administration to goats

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Objective—To evaluate the pharmacokinetics of a novel commercial formulation of ivermectin after administration to goats.

Animals—6 healthy adult goats.

Procedure—Ivermectin (200 µg/kg) was initially administered IV to each goat, and plasma samples were obtained for 36 days. After a washout period of 3 weeks, each goat received a novel commercial formulation of ivermectin (200 µg/kg) by SC injection. Plasma samples were then obtained for 42 days. Drug concentrations were quantified by use of high-performance liquid chromatography with fluorescence detection.

Results—Pharmacokinetics of ivermectin after IV administration were best described by a 2-compartment open model; values for main compartmental variables included volume of distribution at a steady state (9.94 L/kg), clearance (1.54 L/kg/d), and area under the plasma concentration–time curve (AUC; 143 [ng•d]/mL). Values for the noncompartmental variables included mean residence time (7.37 days), AUC (153 [ng•d]/mL), and clearance (1.43 L/kg/d). After SC administration, noncompartmental pharmacokinetic analysis was conducted. Values of the variables calculated by use of this method included maximum plasma concentration (C_{max}; 21.8 ng/mL), time to reach C_{max} (3 days), and bioavailability (F; 91.8%).

Conclusions and Clinical Relevance—The commercial formulation used in this study is a good option to consider when administering ivermectin to goats because of the high absorption, which is characterized by high values of F. In addition, the values of C_{max} and time to reach C_{max} are higher than those reported by other investigators who used other routes of administration. (*Am J Vet Res* 2006;67:323–328)

Ivermectin is a semisynthetic derivative of avermectin B_1 and consists of an 80:20 mixture of the equipotent homologous 22,23 dehydro B_{1a} and B_{1b}.[1] Ivermectin has a broad spectrum of activity against a wide array of endoparasites and ectoparasites in livestock (cattle, sheep, goats, horses, and pigs), pets, wild animals, and fish. Because of its low toxicity, high efficiency, and safety, this compound is also used as an antiparasitic agent in humans, mainly as a treatment for people with onchocerciasis.[1-4,a]

Received April 15, 2005.
Accepted June 17, 2005.
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The rational use of a drug requires knowledge of its basic pharmacokinetics in the animal species in which the drug will be used. Although many pharmacokinetic investigations have been performed in animals after administration of ivermectin by various routes, such information is scarce for ivermectin administration to goats. The authors are not aware of any reports describing pharmacokinetics of ivermectin after IV administration to goats and are aware of only 2 reports[5,6] describing pharmacokinetics after SC administration. The SC route is one of the most commonly used routes of administration.

The characterization of ivermectin pharmacokinetics can be used to predict and optimize its efficacy against endoparasites and ectoparasites.[7] Pharmacokinetic behavior of ivermectin differs on the basis of the route of administration, the vehicle in which this compound is formulated, and the animal species.[8-12] Thus, all of these factors could contribute to differences in the clinical efficacy of the drug.

Drug manufacturers typically do not provide specific dosage recommendations for the use of ivermectin in goats. Thus, ivermectin use in this species is currently based on data extrapolated from other ruminant species, particularly sheep.

The purpose of the study reported here was to evaluate the pharmacokinetics of a novel commercial formulation of ivermectin after SC administration to goats. The SC route is recommended for the administration of this formulation. In addition, ivermectin was administered IV to the same goats to enable us to establish elimination kinetics and F of this compound.

Materials and Methods

Animals—Six healthy nonlactating adult female Alpine goats were used in the study. Goats were 4 years old and weighed 45.5 to 62.0 kg. Health of the goats was closely monitored before and throughout the study.

The goats were fed daily. They were provided alfalfa hay mixed with straw and concentrate and had unlimited access to fresh water. Goats were housed indoors in an adequately ventilated building. Goats were housed under these conditions for 2 weeks before drug administration to allow them to acclimate to their environment, and they were maintained in these housing conditions until the end of the experiment to

F	Bioavailability
C_{max}	Maximum plasma ivermectin concentration
t_{max}	Time to reach C_{max}
AUC	Area under the plasma concentration–time curve
$t_{1/2}$	Half-life
VD_{ss}	Volume of distribution at steady state
k_{12}	Apparent first-order transfer rate constant from the central compartment to the peripheral compartment

prevent stress situations. Protocols and procedures were approved by the Institutional Animal Care and Use Committee of the University of Leon.

Study design and collection of blood samples—A single dose of ivermectin[b] (200 µg/kg) was initially administered to each goat in the left jugular vein. To facilitate administration, ivermectin was dissolved in a mixture (60:40 [vol:vol]) of propylene glycol:glycerol formal containing 5% polyvinylpyrrolidone. Blood samples (5 mL) were collected from both jugular veins into heparin-coated vaccum tubes[c] before (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 sample was collected on day 36 after IV administration, the same goats were administered a single dose of a commercial formulation of ivermectin[d] at the dosage (200 µg/kg) recommended by the manufacturer. The ivermectin was administered by SC injection in the shoulder area of each goat. Blood samples (5 mL) were collected from both jugular veins into heparin-coated vaccum tubes[c] before (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.

Preparation of plasma samples—Immediately after blood samples were collected, they were centrifuged at 3,000 X g for 20 minutes. Plasma was harvested and stored at –80°C until assayed. All samples were analyzed within 60 days after they were obtained.

Chemical extraction and derivatization—Extraction of ivermectin from plasma samples was performed in accordance with a validated method.[13] Briefly, 16 µL of internal standard (doramectin, 0.1 µg/mL to 100 µL) was added to plasma. The mixture was vigorously vortexed for 30 seconds. Then, 500 µL of methanol chilled to –30°C was added. This new mixture was extracted by shaking for 30 seconds followed by incubation at –30°C for 10 minutes. After centrifugation (16,000 X g for 12 minutes at 4°C), the upper phase was evaporated at 50°C under a gentle stream of nitrogen gas.

For derivatization, the dried residue was resuspended in 100 µL of a mixture (1:1 [vol:vol]) of N-methylimidazole:acetonitrile. Subsequently, 150 µL of a mixture (1:2 [vol:vol]) of trifluoroacetic anhydride:acetonitrile was added. The mixture was allowed to react (vortexed for 30 seconds), and the solution was then injected into a chromatograph (2 injections; 100 µL/injection).

Chromatographic conditions—Plasma concentrations of ivermectin were measured by use of high-performance liquid chromatography with fluorescence detection in accordance with a validated procedure reported elsewhere.[13] The mobile phase consisted of 0.2% acetic acid:methanol:acetonitrile (5:45:50 [vol:vol:vol]). Flow rate of the mobile phase was 2 mL/min. The fluorescent derivatives of ivermectin were detected at an excitation wavelength of 365 nm and an emission wavelength of 475 nm.

Chromatography was performed on a high-performance liquid chromatography system[e] equipped with a controller pump,[f] a scanning fluorescence detector,[g] and an auto sampler.[h] A C18 reverse-phase column[i] (140 X 3.9 mm; particle size, 5 µm) was used. Acquisition of chromatography data was performed by use of a commercially available software package.[j]

Interday and intraday accuracy and precision were within 10%. The limits of quantification and of detection, which were determined in accordance with equations described elsewhere,[13] were 0.175 and 0.063 ng/mL, respectively. 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. Our mean extraction recovery from plasma is similar to that obtained by other authors[11,12,14-18] (values for those studies ranged from 77.7% to 93.2%).

Pharmacokinetic analysis—Pharmacokinetic analysis was performed by use of a compartmental as well as a noncompartmental description of the observed data. For compartmental analysis, plasma ivermectin concentration–time patterns were separately fit to the following exponential equation:

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

where C_p is the plasma ivermectin concentration, n is the number of exponential terms, C_i is the y-intercept, λ_i is the slope of each of n first-order rate processes, e is the exponential function (base e), and t is time. The pharmacokinetic model best describing the plasma concentration–time curves of ivermectin was determined by use of a computer program.[k] Equations were fitted to the data by use of a weighting factor (ie, $1/C^2$, where C^2 is the square of experimental concentrations), and the optimum number of first-order rate processes was determined by the use of Akaike criterion[19] and graphic analysis of weighted residuals. Other compartmental variables were calculated by the use of standard methods.[20]

For noncompartmental analysis, we used the same computer program as for the compartmental analysis. Equations described elsewhere[20] were also used to calculate the model-independent pharmacokinetic variables. Values for C_{max} and t_{max} were obtained directly from the plasma concentration–time curves. The fraction of dose absorbed (ie, F) was calculated by use of the AUC for each route of administration by use of the following equation:

$$F = (AUC_{SC}/AUC_{IV}) \times 100$$

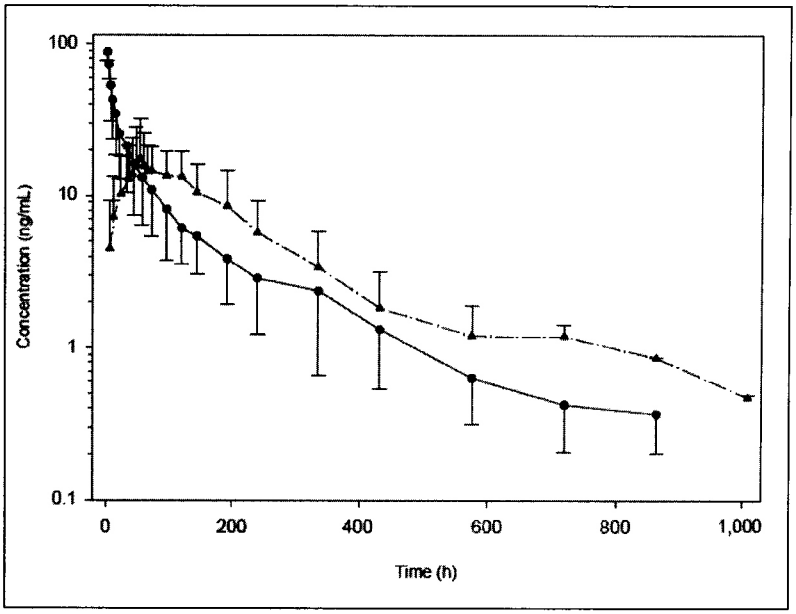

Figure 1—Mean ± SD plasma concentrations of ivermectin after a single dose (200 µg/kg) was administered IV (circles) and SC (triangles) to 6 goats.

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

Variable	Mean ± SD	Range
A (ng/mL)	78.3 ± 39.9	34.5–147.0
B (ng/mL)	9.96 ± 7.08	2.84–22.80
α (/d)	2.17 ± 2.73	0.54–7.67
β (/d)	0.108 ± 0.033	0.046–0.132
AUC ([ng•d]/mL)	143.0 ± 56.4	96.3–253.7
Cl (L/kg/d)	1.54 ± 0.43	0.79–2.08
VD_c (L/kg)	2.81 ± 1.50	1.25–5.36
VD_{ss} (L/kg)	9.94 ± 4.70	4.36–18.50
VD_a (L/kg)	16.5 ± 9.6	6.0–34.5
$t_{1/2\alpha}$ (d)	0.651 ± 0.413	0.090–1.280
$t_{1/2\beta}$ (d)	7.36 ± 3.77	5.27–14.90
C_0 (ng/mL)	88.3 ± 42.9	37.3–160.1

A = The α zero-time intercept. B = The β zero-time intercept. α = Apparent first-order disposition rate constant for the α phase. β = Apparent first-order disposition rate constant for the β phase. Cl = Total body clearance. VD_c = Apparent volume of distribution in the central compartment. VD_a = Volume of distribution of the area. $t_{1/2\alpha}$ = Half-life associated with α phase. $t_{1/2\beta}$ = Half-life associated with β phase. C_0 = Sum 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 ivermectin (200 µg/kg) to 6 goats.

Variable	Mean ± SD	Range
λ (/d)	0.083 ± 0.050	0.030–0.169
AUC ([ng•d]/mL)*	153.0 ± 58.3	103.0–267.0
AUMC ([ng•d^2]/mL)	1,107 ± 449	487–1,693
MRT (d)	7.37 ± 2.72	4.75–12.50
Cl (L/kg/d)*	1.43 ± 0.40	0.75–1.95
VD_{ss} (L/kg)	10.50 ± 4.63	4.31–18.40
VD_a (L/kg)	24.6 ± 15.8	4.5–47.7
$t_{1/2\lambda}$ (d)	11.60 ± 7.37	4.11–23.20

*Value differs significantly ($P < 0.05$) from the corresponding value determined by use of compartmental analysis.

λ = Elimination rate constant. AUMC = Area under the first moment curve. MRT = Mean residence time. $t_{1/2\lambda}$ = Half-life associated with λ phase.

See Table 1 for remainder of key.

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

Variable	Mean ± SD	Range
AUC ([ng•d]/mL)	144.0 ± 70.2	77.0–268.0
MRT (d)	8.25 ± 2.95	5.15–12.10
MAT (d)	0.88 ± 4.47	0.02–5.47
VD_a/F (L/kg)	12.8 ± 6.6	4.3–22.9
Cl (L/kg/d)	1.43 ± 0.40	0.75–1.95
$t_{1/2\lambda}$ (d)	5.57 ± 2.41	2.72–8.87
C_{max} (ng/mL)	21.8 ± 12.8	14.2–47.0
t_{max} (d)	3.00 ± 1.29	1.50–5.00
F (%)	91.8 ± 17.4	69.8–113.0

MAT = Mean absorption time.

See Tables 1 and 2 for remainder of key.

where AUC_{SC} is the AUC after SC administration and AUC_{IV} is the AUC after IV administration.

Statistical analysis—All pharmacokinetic variables were calculated for each goat, and values 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 computer program[1] was used for all statistical analyses.

Results

The goats tolerated ivermectin administration well. No adverse effects were observed in any of the goats after IV or SC administration of ivermectin.

Compartmental analysis revealed that the pharmacokinetics of ivermectin were best described by a 2-compartment open model for IV administration and by a 1-compartment open model with first-order absorption for SC administration (**Figure 1**). However, we considered the noncompartmental analysis to be the best option to evaluate the kinetics of this drug after SC administration to goats because the precision of the estimates obtained by compartmental analysis for several variables was not good.[21,22]

Compartmental analysis after IV administration provided estimates of pharmacokinetic variables that indicated the ivermectin disappeared slowly from plasma with a mean value for the $t_{1/2}$ of the α phase of 0.651 days and a $t_{1/2}$ of the β phase of 7.36 days (**Table 1**). Also, the mean value for the VD_{ss} was 9.94 L/kg, total body clearance was 1.54 L/kg/d, and AUC was 143 (ng•d)/mL.

The main noncompartmental pharmacokinetic variables determined after IV administration of ivermectin revealed the mean value for mean residence time was 7.37 days, AUC was 153 (ng•d)/mL, and total body clearance was 1.43 L/kg/d (**Table 2**). Significant differences were found between values for AUC and total body clearance obtained by compartmental and noncompartmental methods.

Analysis of noncompartmental pharmacokinetic variables obtained after SC administration of the commercial formulation of ivermectin indicated that ivermectin plasma concentrations increased slowly to reach a C_{max} of 21.8 ng/mL, with a t_{max} of 3 days (**Table 3**). The F of this formulation was high, with a mean value of 91.8%. The value obtained for the mean absorption time (0.88 days) also indicated that the absorption of ivermectin was slow.

Discussion

Although several investigators have studied the pharmacokinetics of ivermectin,[8,11,12,16,17,18] few of these studies have been performed in goats. Thus, there is a lack of pharmacokinetic information of this antiparasitic drug in this species. In this sense, there are no data available describing the pharmacokinetics of ivermectin when administered IV to goats, and we are aware of only 2 studies[5,6] in which investigators evaluated the pharmacokinetics of ivermectin after SC administration to goats, although they did not conduct a complete pharmacokinetic study from the compartmental and noncompartmental point of view.

In 1 study,[14] the distribution of ivermectin was examined in 4-month-old French Alpine goats after SC administration at a dosage of 200 µg/kg. Plasma concentrations were determined on days 2, 7, and 17. The

values reported are higher for day 2 than the values reported in our study, but the values from that study are lower on days 7 and 17, compared with the values reported here. In addition, goats used in that study were experimentally infected with *Trichostrongylus colubriformis*.

In the study reported here, we found that ivermectin disappeared slowly from plasma after IV administration and tended to distribute and accumulate in the peripheral compartment. This was evident from the values obtained for the ratio of k_{12} to the apparent first-order transfer rate constant from the peripheral compartment to the central compartment and the ratio of k_{12} to the apparent first-order elimination rate constant from the central compartment, as well as the fact that the value calculated for the apparent volume of distribution in the peripheral compartment was higher than the apparent volume of distribution in the central compartment.

The value obtained for total body clearance of ivermectin after IV administration (1.5 L/kg/d) reflects that the process of elimination is slow. This value was approximately 5-fold higher than the value reported[23] in cattle for this route of administration. Because clearance for IV administration and clearance and F for SC administration are the only determinants of overall exposure, it can be deduced that for the same dose administered to goats and cattle (ie, 200 µg/kg), the overall exposure is approximately 4 to 5 times higher in cattle than in goats. Therefore, to obtain an exposure similar to that obtained for cattle, the dose for goats should be massively increased. This kind of consideration could explain the so-called worm resistance reported for goats.

The VD_{ss} value is higher in goats (compartmental value, 9.94 L/kg; noncompartmental value, 10.5 L/kg) than in cattle (2.72 L/kg). This fact could explain the reason that for a specified total AUC (which is controlled by clearance), the plasma concentrations (which govern transfer of ivermectin to the site of action) are relatively low in goats. This fact could also be an explanation, at least in part, for the apparent weak efficacy reported for ivermectin in goats, especially when the nominal dose is not administered because of poor compliance.

The value obtained for volume of distribution of the area (16.5 L/kg) was much higher than the value obtained for VD_{ss} (9.94 L/kg). This suggests that a large fraction of ivermectin was eliminated during the distributional phase.

Analysis of the results reported here confirms that the 1-compartment model best describes the pharmacokinetics of ivermectin after SC administration. Other authors[5] have also used this model to describe the pharmacokinetics of ivermectin (200 µg/kg) administered to lactating female crossbred goats.

The mean ± SD $t_{1/2}$ of absorption reported in another study[5] was 1.21 ± 0.58 days. That value was extremely similar to the one calculated in the study reported here (1.05 ± 0.603 days). Data obtained for the $t_{1/2}$ of absorption in goats by use of intraruminal administration of ivermectin (200 µg/kg) was lower (0.37 and 0.36 days, respectively) in lactating Murciano-Granadina goats from which food was withheld for 36 hours before treatment and for goats that were provided ad libitum access to feed.[15] In other ruminant species in which ivermectin was administered SC at the same dosage used in our study, the value for the $t_{1/2}$ of absorption ranged from 0.5 to 2.02 days.[16,17,24]

The mean ± SD value for C_{max} obtained in our group of goats (compartmental, 14.0 ± 8.96 ng/mL; noncompartmental, 21.8 ± 12.8 ng/mL) is higher than the value obtained in another study[5] (6.12 ± 1.15 ng/mL). When small doses of ivermectin were administered SC to lactating goats parasitized with *Przhevalskiana silenus*, values for C_{max} were 1.78 ± 0.67 ng/mL and 2.69 ± 0.86 ng/mL for dosages of 5 and 10 µg/kg, respectively.[6] In that study, goats were 0.5 to 3 years old and were fed grass and hay. When other routes of administration are used, the values of C_{max} are variable. After oral administration of ivermectin (200 µg/kg) to lactating crossbred goats,[25] the C_{max} was 15.9 ng/mL. The C_{max} after topical application of various doses of ivermectin was 3.85 ng/mL (500 µg/kg), 0.074 ± 0.013 ng/mL (10 µg/kg), and 0.073 ± 0.035 ng/mL (500 µg/kg).[6] Finally, the C_{max} obtained in goats from which food was withheld for 36 hours before intraruminal administration of ivermectin was 9.34 ± 1.44 ng/mL, compared with 10.6 ± 1.26 ng/mL in goats that had ad libitum access to feed.[15] In studies[8,17] in cattle, values of C_{max} after SC administration of ivermectin at the same dosage used in the study reported here ranged from 13 to 84 ng/mL.

The mean ± SD t_{max} in goats in 1 study[5] was 2.85 ± 0.89 days. Our data (compartmental, 2.81 ± 1.37 days; noncompartmental, 3.00 ± 1.29 days) are extremely similar to that value. However, they differ considerably from those reported in another study[6] in which it was indicated that t_{max} was 0.33 days for 2 dosages of ivermectin (5 or 10 µg/kg). Regarding other routes of administration, t_{max} was 0.5 days after oral administration and 1 day after topical application.[25] By use of topical administration, other investigators[6] found that t_{max} was 0.33 days. A t_{max} of 1.30 ± 0.14 days was calculated for goats from which food was withheld for 36 hours before intraruminal administration, compared with 1.21 ± 0.10 days for goats that were allowed ad libitum access to feed.[15] Values of t_{max} obtained in other ruminants after SC administration of the same dose (200 µg/kg) ranged from 1 to 5 days.[8,17,18,26]

The mean ± SD AUC values obtained in our study (compartmental, 135 ± 69.9 [ng•d]/mL; noncompartmental, 144 ± 70.2 [ng•d]/mL) are higher than the AUC obtained after administration of the same dose to cattle[5] (60.0 ± 13.7 [ng•d]/mL). When ivermectin was administered to goats at dosages of 5 and 10 µg/kg, AUC was 2.51 and 3.38 (ng•d)/mL, respectively.[6] On the other hand, in another study,[25] oral administration of the same dose used in our study resulted in an AUC that was lower (21.5 ± 3.36 [ng•d]/mL) than the value reported here. Topical application of a higher dose (500 µg/kg) in that study[25] also resulted in an AUC that was lower (13.2 ± 2.96 [ng•d]/mL) than the value

reported here. The AUC was 34.4 ± 7.74 (ng•d)/mL in goats from which food was withheld for 36 hours before intraruminal administration, compared with 34.6 ± 2.62 (ng•d)/mL in goats allowed ad libitum access to feed before intraruminal administration.[15] These values are also lower than the AUC reported here. The SC administration of ivermectin (200 µg/kg) to cattle[11,12,17] provides AUC values that range from 206 to 459 (ng•d)/mL, which are higher than the value reported here.

Mean ± SD value for mean residence time (8.25 ± 2.95 days) determined in our study is similar to the value reported after SC administration[5] (7.85 ± 1.42 days) and higher than those obtained after intraruminal administration[15] (2.8 ± 0.2 days and 2.6 ± 0.1 days, respectively, for goats from which food was withheld for 36 hours before administration and goats that were allowed ad libitum access to food before administration). The data reported by other authors[17,27] after SC administration of ivermectin to cattle at the same dose used in our study ranged from 4.3 to 9.9 days.

Finally, the mean ± SD $t_{1/2}$ of elimination calculated in the study reported here (compartmental, 4.75 ± 1.86 days; noncompartmental, 5.57 ± 2.41 days) is slightly higher than the value reported[5] for the SC route (4.03 ± 0.9 days). Both values reported here are higher than those obtained after intraruminal administration in goats from which food was withheld for 36 hours before treatment and goats that were allowed ad libitum access to feed before treatment (1.24 ± 0.04 days and 1.18 ± 0.03 days, respectively).[15] In cattle treated by SC administration of ivermectin (200 µg/kg),[8,27] the elimination $t_{1/2}$ ranged from 2.0 to 9.7 days.

On the basis of the aforementioned results, it can be determined that there is great variability in ivermectin pharmacokinetics. This has been attributed to several factors, such as differences in breed, age, weight, body condition, prior feeding, number of samples collected, and time of collection of the last sample. These factors can affect plasma concentrations of ivermectin and, at least in part, can explain the differences between our results and those of other authors. In addition, it is important to remember that the use of various formulations of ivermectin can be one of the major factors in determining these differences.

We conclude that the commercial formulation used in the study reported here is a good option to consider when administering ivermectin to goats because of the high absorption, which is characterized by high values of F. In addition, the values of C_{max} and t_{max} obtained are higher than those reported by other authors who used other routes of administration.

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