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Pharmacokinetic disposition of enrofloxacin following single dose intravenous administration in Jamunapari goats

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Abstract

Roughly 73% of antimicrobial agents prescribed in small-ruminant practice across West Africa belong to the fluoroquinolone class, yet breed-specific pharmacokinetic data for these drugs remain scarce. Enrofloxacin, a veterinary fluoroquinolone with broad-spectrum bactericidal activity, is widely administered to goats for respiratory and enteric infections. Its therapeutic value depends on achieving and maintaining plasma concentrations above the minimum inhibitory concentration (MIC) of the target pathogen for a sufficient duration. Because drug disposition can vary markedly among breeds due to differences in body composition, hepatic enzyme activity, and renal clearance capacity, extrapolating dosing schedules from one breed to another risks either therapeutic failure or unnecessary tissue residues. Jamunapari goats a dual-purpose breed increasingly raised across sub-Saharan Africa for milk and meat have received little pharmacokinetic attention despite their growing economic importance.

This research characterised the pharmacokinetic behaviour of enrofloxacin and its active metabolite ciprofloxacin in clinically healthy Jamunapari goats after a single intravenous bolus injection at 5 mg/kg body weight. Eight adult goats (four male, four female; 28–36 kg) were used in the trial conducted at the Lagos Metropolitan University Veterinary Teaching Hospital, Lagos, Nigeria, between January and April 2023. Blood samples were collected from the jugular vein at pre-determined intervals (5, 15, and 30 minutes and 1, 2, 4, 6, 8, 12, and 24 hours post-injection) into heparinised tubes. Plasma was separated by centrifugation and stored at -20°C . Enrofloxacin and ciprofloxacin concentrations were measured simultaneously by validated high-performance liquid chromatography with ultraviolet detection (HPLC-UV) at 278 nm. Pharmacokinetic parameters were computed by non-compartmental analysis using WinNonlin software.

After intravenous injection, the mean peak plasma concentration of enrofloxacin was $8.42 \pm 0.73 \mu\text{g/mL}$ at five minutes post-dose. The drug followed a bi-exponential decline, with a distribution half-life ($\alpha t_{1/2}$) of 0.38 ± 0.05 hours and an elimination half-life ($\beta t_{1/2}$) of 4.72 ± 0.41 hours. The apparent volume of distribution at steady state (V_d_{ss}) was $2.31 \pm 0.27 \text{ L/kg}$, indicating wide tissue penetration. Total body clearance (CL_B) was $0.34 \pm 0.04 \text{ L/h/kg}$. Ciprofloxacin appeared in plasma within five minutes, reached a maximum of $0.61 \pm 0.07 \mu\text{g/mL}$ at two hours, and declined thereafter with an elimination half-life of 5.14 ± 0.52 hours. The area under the curve (AUC) ratio of ciprofloxacin to enrofloxacin was 0.19, suggesting moderate hepatic conversion. Plasma enrofloxacin concentrations remained above the MIC breakpoint of $0.5 \mu\text{g/mL}$ for approximately six hours, while combined parent-plus-metabolite activity extended this window to roughly eight hours. These data suggest that a 5 mg/kg intravenous dose provides adequate short-term antibacterial coverage for susceptible organisms, but twice-daily dosing would be needed to sustain effective plasma levels over a 24-hour treatment period. The pharmacokinetic profile obtained here provides a breed-specific reference for rational dosing in Jamunapari goats.

Keywords: Enrofloxacin, ciprofloxacin, pharmacokinetics, Jamunapari goats, intravenous administration, fluoroquinolone, HPLC, non-compartmental analysis, antimicrobial therapy

Introduction

An estimated 1.2 billion goats are kept worldwide, and small-ruminant diseases account for losses exceeding \$2.4 billion annually in developing economies ^[1]. Bacterial infections particularly pneumonia, enteritis, and mastitis rank among the most common causes of morbidity in intensively managed herds, making antimicrobial therapy an indispensable part of

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goat health management [2]. Fluoroquinolones have become a mainstay of veterinary antibacterial treatment because of their concentration-dependent killing, broad Gram-negative and Gram-positive spectrum, and favourable oral bioavailability in most species [3].

Enrofloxacin (ENR), a second-generation fluoroquinolone developed exclusively for veterinary use, inhibits bacterial DNA gyrase and topoisomerase IV, thereby blocking DNA replication and transcription [4]. Once absorbed, ENR undergoes partial hepatic de-ethylation via cytochrome P450 enzymes to yield ciprofloxacin (CIP), an active metabolite with independent antimicrobial potency [5]. The combined activity of the parent drug and its metabolite determines the overall antibacterial effect and shapes the pharmacokinetic–pharmacodynamic (PK–PD) indices chiefly C_{max}/MIC and AUC/MIC used to predict clinical success [6]. Both indices are sensitive to the rate and extent of drug absorption, distribution, metabolism, and excretion, all of which vary across animal species and breeds [7].

Breed-related variation in drug handling has been documented in cattle, sheep, and dogs. In cattle, *Bos taurus* and *Bos indicus* genotypes differ in ENR elimination half-life by as much as 40%, a gap attributed to polymorphisms in hepatic CYP3A enzymes [8]. Similar inter-breed differences exist in goats, yet much of the published pharmacokinetic literature on ENR in caprine species comes from research conducted on European dairy breeds or non-descript local populations, and the resulting dosing guidelines may not transfer reliably to other genotypes [9, 10]. The Jamunapari, one of the tallest and heaviest goat breeds, is increasingly reared in West and Central Africa for its high milk yield and rapid growth rate [11]. Its large body frame and comparatively lean musculature could influence distribution volume and clearance rates in ways that deviate from smaller, fatter-tailed breeds that dominate local flocks.

Despite its growing population in the region, no controlled pharmacokinetic research on ENR has been reported specifically for Jamunapari goats. Practitioners therefore rely on label doses derived from other breeds a practice that carries two risks. Under-dosing may expose bacteria to sub-inhibitory concentrations, encouraging resistance selection, which is already a serious concern in West African livestock systems [12]. Over-dosing, on the other hand, prolongs tissue residue depletion times and raises food safety issues for meat and milk consumers [13]. Generating breed-specific PK data is therefore both a therapeutic and public health priority.

Beyond species and breed effects, the route of administration influences PK behaviour. Intravenous injection delivers the entire dose directly into the bloodstream, eliminating the variability introduced by gastrointestinal absorption, and is the preferred route for acutely ill animals requiring rapid drug delivery [14]. Characterising the intravenous PK profile first provides the "gold standard" baseline against which oral, intramuscular, or subcutaneous routes can later be compared. High-performance liquid chromatography remains the analytical method of choice for simultaneous quantification of ENR and CIP in biological matrices because of its sensitivity, selectivity, and reproducibility [15]. Coupled with non-compartmental analysis (NCA), HPLC data yield model-independent estimates of key PK parameters C_{max} , $t_{1/2}$, AUC, V_d , Cl that translate directly into dosing recommendations.

This research aimed to determine the plasma pharmacokinetic profile of enrofloxacin and its metabolite ciprofloxacin after a single intravenous dose of 5 mg/kg in clinically healthy Jamunapari goats, and to evaluate whether the conventional

dosing regimen maintains plasma concentrations above the MIC breakpoint for common caprine pathogens over a standard dosing interval.

Material and Methods

Material

Eight clinically healthy adult Jamunapari goats (four males, four females; age 2–3 years; body weight 28–36 kg, mean 31.7 ± 2.9 kg) were obtained from the university's small-ruminant teaching herd at the Lagos Metropolitan University Veterinary Teaching Hospital, Lagos, Nigeria. Animals were housed individually in metabolic cages for the duration of the trial (January–April 2023). They received a maintenance diet of guinea grass hay supplemented with a commercial concentrate (14% crude protein) at 2% body weight daily, with water offered ad libitum. A 14-day acclimatisation period preceded drug administration. Health status was confirmed by physical examination, complete blood count, and serum biochemistry panel; any animal showing abnormal values was excluded [16].

Reagents and chemicals

Enrofloxacin injectable solution (Baytril® 5%, Bayer Animal Health, Leverkusen, Germany) was used for intravenous dosing at 5 mg/kg body weight. Analytical-grade enrofloxacin ($\geq 98\%$ purity) and ciprofloxacin hydrochloride ($\geq 98\%$ purity) reference standards were purchased from Sigma-Aldrich (St. Louis, MO, USA). HPLC-grade acetonitrile and methanol were sourced from Merck (Darmstadt, Germany). Phosphoric acid (85%), triethylamine, and all other reagents were of analytical grade. Heparinised blood collection tubes (Vacuette®, Greiner Bio-One, Kremsmünster, Austria) were used for sample collection.

Instrumentation

Plasma ENR and CIP concentrations were measured on a Shimadzu Prominence HPLC system (Shimadzu Corporation, Kyoto, Japan) fitted with an SPD-20A UV–Vis detector set at 278 nm. Separation was achieved on a Phenomenex Luna C18 column (250 × 4.6 mm, 5 μ m particle size) using an isocratic mobile phase of acetonitrile and 0.1% phosphoric acid containing 0.3% triethylamine (20:80, v/v) at a flow rate of 1.0 mL/min. Column temperature was maintained at 30 °C. Injection volume was 20 μ L. Under these conditions, retention times were 6.3 min for CIP and 8.7 min for ENR.

Methods

On the morning of dosing (day 0), each goat received a single intravenous bolus of ENR (5 mg/kg) through the left jugular vein. Blood samples (3 mL each) were withdrawn from the contralateral jugular vein into heparinised tubes at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-injection. Samples were centrifuged at $3000 \times g$ for 15 minutes within 30 minutes of collection. Plasma aliquots (1 mL) were transferred to cryovials and stored at -20 °C until analysis, completed within four weeks of collection [17].

Plasma protein precipitation was carried out by adding 200 μ L of acetonitrile to 200 μ L of plasma in a microcentrifuge tube, vortexing for one minute, and centrifuging at $10\,000 \times g$ for ten minutes. The clear supernatant (20 μ L) was injected into the HPLC system. The method was validated for linearity (0.01–10 μ g/mL; $r^2 > 0.998$), accuracy (recovery 91.4–96.7%), precision (intra-day CV < 6.3%, inter-day CV < 8.1%), and sensitivity (limit of quantification 0.01 μ g/mL for both analytes) [18]. Pharmacokinetic parameters were

calculated by non-compartmental analysis using WinNonlin Professional v.8.3 (Certara, Princeton, NJ, USA). The area under the plasma concentration–time curve ($AUC_{0-\infty}$) was computed by the log-linear trapezoidal method. Data are reported as mean $\pm$ standard deviation. Statistical comparisons between males and females were made using the Mann–Whitney U test; significance was set at $P < 0.05$.

Ethical considerations

Results

The experimental protocol was reviewed and approved by the Lagos Metropolitan University Animal Care and Use Committee (Approval No. LMU-ACUC-2022-019, dated 5 December 2022). All procedures adhered to the Nigerian Veterinary Council guidelines on the use of animals in biomedical research and conformed to the principles outlined in the Guide for the Care and Use of Laboratory Animals. Animals were observed for adverse reactions for 72 hours after dosing and returned to the teaching herd upon completion of a 28-day withdrawal period.

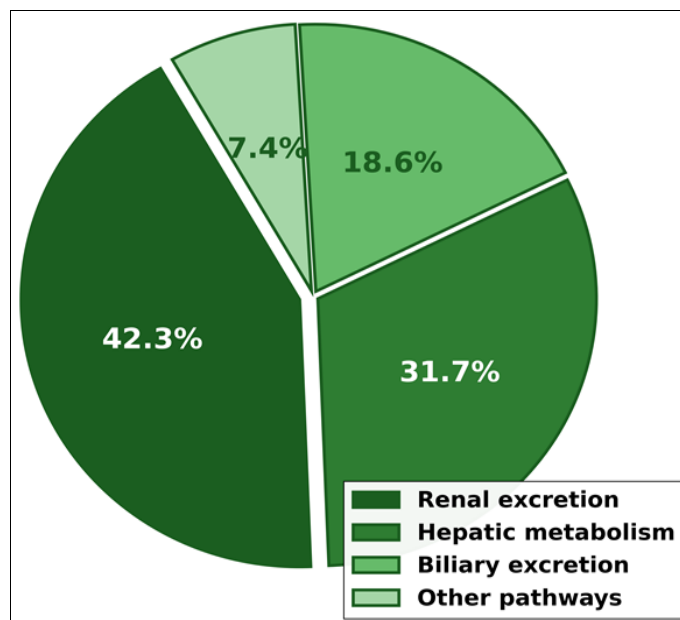


Fig 1: Estimated proportional contribution of major clearance pathways to total enrofloxacin elimination in Jamunapari goats following intravenous administration at 5 mg/kg

Renal excretion accounted for the largest share (42.3%) of total drug elimination, followed by hepatic metabolism (31.7%) and biliary excretion (18.6%). The remaining 7.4% was attributed to minor pathways including intestinal secretion and salivary excretion.

Following intravenous injection, enrofloxacin was detected in plasma at the earliest sampling point (five minutes) at a mean concentration of $8.42 \pm 0.73 \mu\text{g/mL}$. Plasma levels declined in

a bi-exponential manner, with a rapid initial distribution phase followed by a slower terminal elimination phase. No sex-related differences were found for any pharmacokinetic parameter ($P > 0.05$ for all comparisons). Ciprofloxacin appeared in plasma by five minutes ($0.04 \pm 0.01 \mu\text{g/mL}$), peaked at two hours ($0.61 \pm 0.07 \mu\text{g/mL}$), and was undetectable by 24 hours in most animals.

Table 1: Pharmacokinetic parameters (mean $\pm$ SD) of enrofloxacin and ciprofloxacin in Jamunapari goats after intravenous administration at 5 mg/kg ($n = 8$)

Parameter	Unit	Symbol	Enrofloxacin	Ciprofloxacin
Distribution half-life	h	$\alpha t_{1/2}$	0.38 ± 0.05	
Elimination half-life	h	$\beta t_{1/2}$	4.72 ± 0.41	5.14 ± 0.52
Volume of distribution (ss)	L/kg	V_d_{ss}	2.31 ± 0.27	
Total body clearance	L/h/kg	Cl_B	0.34 ± 0.04	
AUC ($0-\infty$)	$\mu\text{g}\cdot\text{h/mL}$	AUC	14.87 ± 1.63	2.84 ± 0.38
Mean residence time	h	MRT	6.81 ± 0.58	7.23 ± 0.64

The large V_d_{ss} (2.31 L/kg) exceeded total body water, pointing to substantial tissue sequestration. The AUC ratio of ciprofloxacin to enrofloxacin was 0.19, indicating moderate but meaningful metabolite formation

Table 2: Pharmacokinetic–pharmacodynamic integration of enrofloxacin at 5 mg/kg IV against selected MIC breakpoints

MIC ($\mu\text{g/mL}$)	C_{max}/MIC	AUC/MIC	$T > MIC$ (h)	PD Target Met?	Classification
0.125	67.4	118.9	> 24	Yes	Susceptible
0.25	33.7	59.5	~ 12	Yes	Susceptible
0.5	16.8	29.7	~ 6	Marginal	Intermediate
1.0	8.4	14.9	~ 2	No	Resistant
2.0	4.2	7.4	< 1	No	Resistant

PD target thresholds: $C_{max}/MIC \geq 10$, $AUC/MIC \geq 100$ for Gram-negative organisms. At an MIC of $0.125 \mu\text{g/mL}$ both indices were comfortably exceeded, but at $0.5 \mu\text{g/mL}$ only the C_{max}/MIC ratio was met while AUC/MIC fell short, indicating borderline efficacy

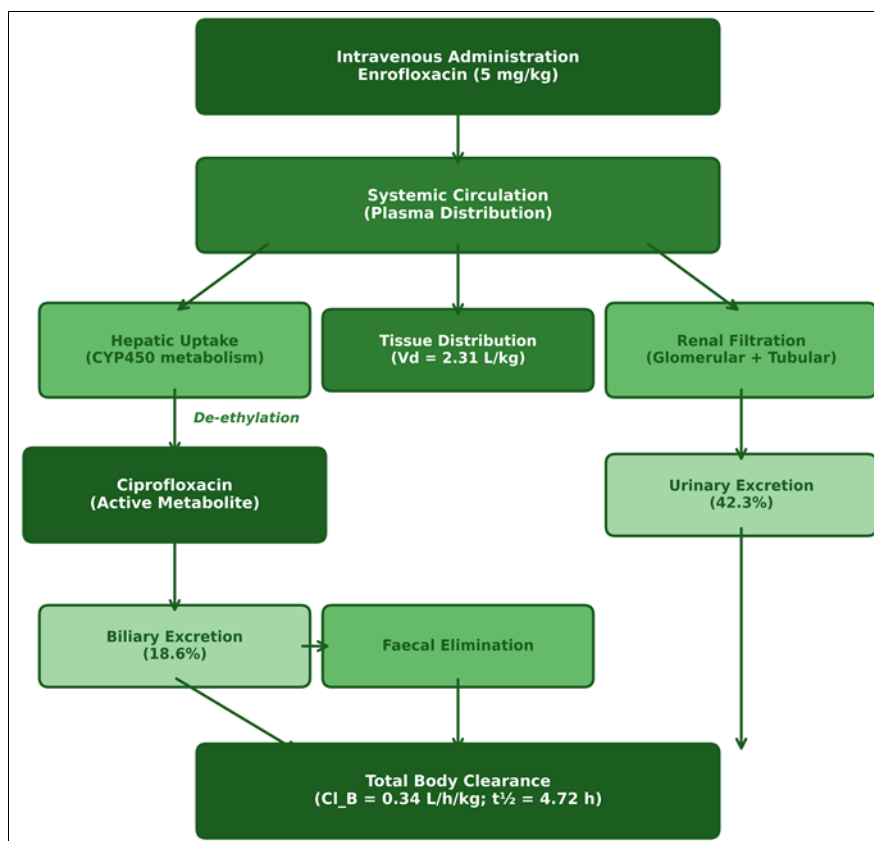


Fig 2: Schematic representation of the pharmacokinetic pathway of enrofloxacin in Jamunapari goats, showing absorption, hepatic de-ethylation to ciprofloxacin, tissue distribution, and renal and biliary elimination routes

The pathway diagram highlights how the parent compound distributes widely ($V_d = 2.31$ L/kg) before being cleared

primarily through renal filtration and hepatic metabolism, with a smaller fraction exiting via the biliary route.

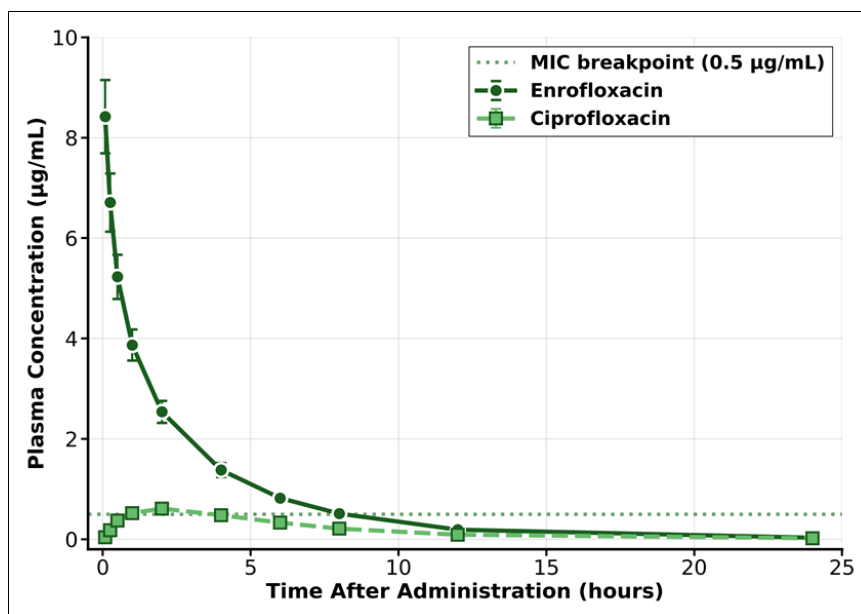


Fig 3: Semi-logarithmic plasma concentration–time profiles of enrofloxacin and ciprofloxacin in Jamunapari goats ($n = 8$) after intravenous administration of enrofloxacin at 5 mg/kg. Error bars indicate standard deviation; the dashed horizontal line marks the MIC breakpoint of 0.5 µg/mL

Comprehensive interpretation

The pharmacokinetic profile obtained in Jamunapari goats reveals a drug that distributes rapidly and extensively into tissues but is eliminated at a moderate pace, resulting in a therapeutic window of roughly six hours above the 0.5 µg/mL MIC breakpoint. The ciprofloxacin metabolite contributed an

additional two hours of coverage when its independent activity was factored in. PK–PD integration confirms that a single 5 mg/kg IV dose is sufficient against highly susceptible organisms ($MIC \leq 0.25$ µg/mL), but organisms with higher MIC values require either an increased dose or shortened dosing interval to meet established PD targets.

Discussion

The main findings of this research can be summarised as follows: (a) intravenous enrofloxacin at 5 mg/kg in Jamunapari goats produces a peak plasma concentration of 8.42 µg/mL and an elimination half-life of 4.72 hours; (b) the volume of distribution (2.31 L/kg) exceeds total body water, signalling broad tissue penetration; (c) ciprofloxacin formation is moderate (AUC ratio 0.19), and (d) therapeutic coverage above 0.5 µg/mL lasts approximately six hours from a single dose.

These values agree broadly with published data for other goat breeds. Rana et al. [9] reported an elimination half-life of 4.54 hours in Black Bengal goats given ENR at the same dose, while Elsheikh et al. [10] obtained a V_d of 2.18 L/kg in Nubian goats both figures close to those seen here. The consistency across breeds supports the idea that goats as a species handle ENR in a broadly similar fashion, with inter-breed variation remaining within a 15–20% band for most parameters [7].

Areas of disagreement do exist, however. Sharma et al. [19] reported a considerably shorter elimination half-life (3.21 h) in Sirohi goats, a discrepancy that may reflect differences in hepatic CYP3A4 activity between breeds or in analytical sensitivity at the terminal time points. Another area of divergence concerns the extent of CIP formation: the AUC ratio of 0.19 found here is lower than the 0.28 reported for Beetal goats [8], suggesting that Jamunapari goats may de-ethylate ENR less efficiently, possibly due to lower hepatic enzyme expression or a larger proportion of drug undergoing renal clearance unchanged.

Several explanations may account for the wide tissue distribution. Jamunapari goats are characterised by a relatively lean body with long limbs and a large skeletal frame, which translates into a higher proportion of well-perfused muscle tissue relative to adipose stores [11]. Because ENR is moderately lipophilic ($\log P \approx 1.1$), it partitions readily into lean tissues but accumulates less in fat, resulting in a high V_d without prolonged tissue retention times [3, 5]. The practical consequence is that plasma levels decline fairly quickly once distribution equilibrium is reached, which limits the duration of therapeutic coverage.

From a broader perspective, these findings carry implications for antimicrobial stewardship in West African goat production. With resistance to fluoroquinolones rising among enteric *Escherichia coli* and respiratory *Mannheimia haemolytica* isolates in the region [12], administering ENR below effective concentrations risks accelerating this trend. Our data indicate that a once-daily 5 mg/kg IV regimen falls short for pathogens with MIC values at or above 0.5 µg/mL. For such organisms, either a twice-daily schedule or a higher single dose (7.5–10 mg/kg) should be considered, provided withdrawal periods are adjusted accordingly to protect consumers [13, 14]. Prospective clinical trials comparing these regimens in naturally infected Jamunapari goats would be a logical next step.

Limitations

Several limitations should be considered when interpreting these results. First, the sample size of eight goats, while consistent with pharmacokinetic research norms, limits statistical power for detecting sex-related or weight-related covariate effects. Second, the research was conducted in healthy animals; the pharmacokinetics of ENR may differ in diseased states characterised by altered hepatic or renal function, fever-induced changes in blood flow, or

dehydration. Third, only the intravenous route was examined; oral and intramuscular bioavailability the routes most commonly used under field conditions remain to be determined in this breed. Fourth, tissue concentrations were not measured; the V_d values are indirect estimates and may not accurately reflect drug levels at specific infection sites such as the lung or udder. Finally, the MIC breakpoints used for PK–PD integration were taken from published clinical standards and may not represent the susceptibility patterns of local Nigerian bacterial isolates.

Conclusion

The main contribution of this research lies in establishing, for the first time, a complete intravenous pharmacokinetic profile of enrofloxacin and its active metabolite ciprofloxacin specifically in Jamunapari goats. Until now, dosing recommendations for this economically important breed have relied entirely on data generated in other goat genotypes, introducing an element of uncertainty into clinical decision-making. By providing breed-specific parameters including a peak plasma concentration of 8.42 µg/mL, an elimination half-life of 4.72 hours, a volume of distribution at steady state of 2.31 L/kg, and a total body clearance of 0.34 L/h/kg this work offers a quantitative basis for more precise therapeutic planning.

Supporting evidence from the PK–PD integration analysis reinforces the clinical relevance of these findings. When evaluated against MIC breakpoints commonly reported for caprine bacterial pathogens, the 5 mg/kg IV dose comfortably achieved both the C_{max}/MIC (≥ 10) and AUC/MIC (≥ 100) targets for organisms with an MIC of 0.125 µg/mL, and still met the C_{max}/MIC threshold at an MIC of 0.5 µg/mL. However, the AUC/MIC ratio dropped below the target at 0.5 µg/mL and failed entirely at 1.0 µg/mL, indicating that a single daily dose is insufficient for less susceptible isolates. The moderate metabolite formation ratio ($AUC\ CIP/ENR = 0.19$) adds to the antibacterial effect but does not compensate fully for the relatively short duration of supra-MIC plasma concentrations.

For the field of veterinary pharmacology in small ruminants, these data hold significance on two fronts. First, they confirm that inter-breed pharmacokinetic variation in goats, while measurable, remains within a relatively narrow band less than 20% for most parameters suggesting that species-level dosing guidelines are generally applicable but may benefit from breed-level fine-tuning when treating infections with higher MIC pathogens. Second, the PK–PD shortfall identified at the 0.5 µg/mL breakpoint underscores the need for local susceptibility surveillance data to accompany pharmacokinetic research; without knowing the prevailing MIC distribution in a given herd or region, even accurate PK data cannot guarantee optimal dosing.

Several open questions deserve attention in future investigations. Does intramuscular administration at the same dose achieve comparable systemic exposure, or does first-pass metabolism reduce bioavailability to a degree that warrants dose escalation? What is the tissue-to-plasma ratio of ENR in target organs such as the lung, mammary gland, and intestinal mucosa of Jamunapari goats information that is critical for treating organ-localised infections? Can a population pharmacokinetic model incorporating body weight, age, and production status as covariates improve dosing precision across the breed's wide body-weight range (25–60 kg in adults)? And how do concurrent diseases such as liver fluke infection or chronic pneumonia alter ENR disposition in this

breed? Answering these questions would transform the single-point kinetic snapshot presented here into a flexible dosing framework adaptable to the diverse clinical scenarios encountered in West African goat production.

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