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ORIGINAL ARTICLE

Pharmacokinetics of robenacoxib following single intravenous, subcutaneous and oral administrations in Baladi goats (*Capra hircus*)

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Abstract

The purpose of this study was to assess the pharmacokinetics of robenacoxib (RX), a COX-2 selective non-steroidal anti-inflammatory drug, in goats after single intravenous (IV), subcutaneous (SC) and oral (PO) administrations. 5-month-old healthy female goats ($n = 8$) were used. The animals were subjected to a three-phase, two-dose (2 mg/kg IV, 4 mg/kg SC, PO) unblinded, parallel study design, with a four-month washout period between the IV and SC treatment, and a one-week period between the SC and PO treatment. Blood was drawn from the jugular vein in heparinized vacutainer tubes at 0, 0.085 (for IV only), 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10 and 24 h. Plasma RX concentrations were measured using HPLC coupled to a UV multiple wavelength detector, and the data were pharmacokinetically analysed using ThothPro™ 4.3 software in a non-compartmental approach. Following IV administration, terminal elimination half-life, volume of distribution and total clearance were 0.32 h, 0.24 L/kg and 0.52 L/h/kg, respectively. For SC and PO, the mean peak plasma concentrations were 2.34 and 3.34 μg/mL at 1.50 and 0.50 h, respectively. The t1/2λz was significantly different between the IV and the extravascular (EV) administrations (0.32 h IV vs 1.37 h SC and 1.63 h PO), suggesting the occurrence of a flip-flop phenomenon. The significant difference in V_d values between IV (0.24 L/kg) and EV (0.95 L/kg SC and 1.71 L/kg; corrected for *F* %) routes might have also triggered the t1/2λz difference. The absolute average SC and PO bioavailability were high (98% and 91%, respectively). In conclusion, the IV administration of RX might not be suitable for goats, due to its short t1/2λz. The EV routes, however, appear to be convenient for the drug's occasional use.

KEYWORDS
coxibs, goats, non-steroidal anti-inflammatory drugs, pain management, pharmacokinetics, robenacoxib

1 | INTRODUCTION

Human populations are significantly impacted by the socioeconomics of goat rearing, particularly in rural and economically underdeveloped areas. Due to its traits, including strong environmental adaptability and the capacity to utilize low-quality natural resources, the goat—whose meat, milk and skin are used by humans—is a significant livestock species around the world (Skapetas & Bampidis, 2016).

There are approximately 2.2 billion sheep and goats in the world. In 2017, it was projected that there were at least 218 million dairy goats in the world. Dairy goat populations have been rising progressively all throughout the world, with massive increases in the 1990s (FAO, 2019). Both established and emerging countries are seeing an increase in demand for dairy goat products. In fact, goat milk and its products are becoming more and more popular due to their healthy and nutritional advantages, which include greater digestibility and lipid metabolism, in addition to their taste, compared to cow milk (Haenlein, 2004). The majority of goats are raised by small-scale farmers outside of specialized production systems. The production of goat milk is notably significant in the Mediterranean region, the Middle East, Eastern Europe and portions of South America, whereas India, Bangladesh, Pakistan and Turkey produce and consume the majority of the world's goat milk (Ribeiro & Ribeiro, 2010). In Lebanon, for instance, more than 6000 families depend on goat herd products including milk, meat and fur for their livelihood (MOA, 2009), with this herd being represented in large part by the local caprine population known as Baladi (95%) and, to a smaller extent, by the Damascus breed (Hajj, 1999; Nehme & Abi Saab, 2003).

As the numbers of goats and the significance of their role as production animals increase, the need to improve and extend the quality of life of these animals is also growing in parallel, especially given the current public pressure for better agricultural practices and enhanced animal welfare (Stuart et al., 2019). Indeed, animal welfare and pain management in farm-animals have become increasingly popular issues of conversation and study among producers, veterinarians and society (Fraser et al., 2013). Many researchers have attempted to provide evidence of beneficial effects of analgesia for routine procedures in cattle and small ruminants. Goats experience varying degrees of pain, resulting either from husbandry operations such as castration, vasectomy and tail docking, or from painful pathologies, whether acute or chronic, such as lameness, mastitis, vaginal prolapse, penis deviation, osteoarthritis, spondylitis and other painful conditions (Galatos, 2011; Plummer & Schleining, 2013).

The ineffective pain management in small ruminants can be blamed on a variety of factors. For instance, there are no non-steroidal anti-inflammatory drugs (NSAIDs) that are approved for use in controlling pain in sheep or goats in the United States and Europe (Lizarraga & Chambers, 2012; Smith et al., 2021). In lieu of an approved product, numerous drugs are used in an off-label manner to reduce pain in goats (Stuart et al., 2019). For such an indication, the most commonly prescribed class of drugs is NSAIDs, including flunixin meglumine, meloxicam, carprofen, ibuprofen, aspirin and phenylbutazone, depending on animal species and class. Dosing, routes of administration and indications for use of NSAIDs in small ruminants are generally extrapolated from the cattle label (Reppert et al., 2019), which may not be safe/effective due to the paucity of knowledge regarding the pharmacokinetics, efficacy and residue depletion of the drugs in these animal species. Therefore, it is essential to comprehend the pharmacokinetics and pharmacodynamics of NSAIDs in goats in order to evaluate the optimal dose and the effectiveness of the drug as well as to reduce adverse drug effects and tissue residues and guarantee a safe food supply to consumers (Reppert et al., 2019).

Robenacoxib (RX) is a highly selective COX-2 inhibitor, belonging to the coxib family. It is used to treat postoperative pain and inflammation in cats and dogs (orthopaedic surgery and soft tissue surgery), as well as pain and inflammation associated with acute and chronic musculoskeletal disorders (EMA, 2018). Given the scarcity of medications available for treating pain in small ruminants, this treatment might be beneficial in goats. However, the pharmacokinetic (PK) and pharmacodynamic (PD) differences between animal species, particularly between ruminants and monogastric animals, necessitate further research to understand the drug's behaviour in the target species. To the best of the authors' knowledge, there have been no previous RX studies in goats. As a result, the goal of this study was to establish the PK of RX after single intravenous (IV; 2 mg/kg), subcutaneous (SC; 4 mg/kg) and oral (PO; 4 mg/kg) administrations.

2 | MATERIALS AND METHODS

2.1 | Chemicals and reagents

The pure powders of RX and diclofenac as the internal standard (IS) with a standard purity of 99.0%, alongside the sodium chloride (NaCl), were purchased from Sigma-Aldrich. High Performance Liquid Chromatography (HPLC)-grade acetonitrile (ACN), methanol (MeOH), and formic acid were obtained from VWR chemicals. Deionized water was produced using a Milli-Q Millipore Water System (Millipore). The mobile phase's aqueous and organic components were combined in the HPLC apparatus after being degassed under pressure. With the aid of a solvent filtration device, the mobile phases were filtered through 0.2 μm cellulose acetate membrane filters (Sartorius Stedim Biotech).

2.2 | Animals and experimental design

Eight, 5-month-old, healthy adult female Baladi goats, with body weights ranging from 16 to 25 kg, were used in the study. In 10 by 10 m stalls with 10 × 30 m outdoor runs attached, animals were group-housed. Bedded on straw, they were provided with feed (alfalfa hay) and water ad libitum. Goats were declared healthy before being enrolled in the study based on a physical examination, hemogram and serum chemical profile, all of which were completed within

3 days of the study's initiation. No recent pharmacological treatment had been administered (2 months), and the goats were parasite-free. To determine the dose to administer, body weights were measured 24 h prior to the drug's administration. The animal experiment was approved by the Lebanese ministry of Agriculture ethical committee, verifying that this study complies with European standards for animal welfare guidelines (study protocol number 1120221).

2.3 | Drug

This trial employed the commercial SC formulation of 20 mg RX per mL (Onsior®, Elanco) and oral tablets containing 40 mg each (Onsior®, Elanco). Because no previous recommendations on the doses in ruminants were published, the doses chosen were based on RX data from cats and dogs, for which the Onsior® tablets are allowed in the European Union for surgical applications at a dose of 2 mg/kg, with a range of 2–4 mg/kg (EMA, 2018).

2.4 | Drug dosing, administration and blood sample collection

A three-phase, two-dose (2 mg/kg IV, 4 mg/kg SC, PO) unblinded, parallel study design, with a four-month washout period between the IV and SC treatment, and a one-week period between the SC and PO treatment, was performed. In phase 1, goats were given a bolus IV injection (1 min) of RX in the right jugular vein at a dose of 2 mg/kg. In phase 2, a SC injection of 4 mg/kg RX was performed behind the right shoulder and above the ribs. The third phase involved carefully weighing and partitioning the grinded RX tablets to form the 4 mg/kg PO doses. Following administration through an oro-ruminal tube with the grinded tablets dissolved in 20 mL of water, the tube was promptly flushed with 100 mL of water. From the left jugular vein, blood samples were drawn using vacutainer lithium heparin tubes (BD) at 0, 0.085 (for IV only), 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10 and 24 h. The blood sampling time points were selected based on the previous pharmacokinetic data in sheep (Fadel et al., 2022). After collection, blood was centrifuged for 10 min at 1500 *g*. The plasma was then separated, transferred in cryovials and stored at −20°C. Within one week following the conclusion of the final phase, plasma samples was analysed.

2.5 | Plasma RX determination

The sample preparation was determined using a published method (Jung et al., 2009), and it was modified according to Fadel et al. (2022). To increase the ionic power of water, 50 mg of NaCl was added to 200 µL of plasma. The plasma was then spiked with 50 µL of an IS solution in MeOH (50 g/mL). 800 mL of ACN was then added. The samples were shaken at 60 oscillations per minute for 10 min after vigorous vortex mixing (30 s) and then centrifuged at 4000 *g* for 10 min. The upper layer was transferred into a clean tube and dried at 45°C while being gently streamed with nitrogen. The residue was dissolved in 120 µL of ACN:H_2O 60:40 (v/v), vortexed for 1 minute, sonicated at 25°C for 10 min and then finally centrifuged at 4000 *g* for 2 min. An aliquot of 50 µL of the upper layer was injected onto the HPLC system for analysis.

The LC Jasco HPLC system included an autosampler (AS2055), ternary gradient system (PU 980), in-line degasser (DG-2080-53) and a UV multiple wavelength detector (MD-1510). Utilizing a Peltier device (CO4062) to maintain the column temperature at 30°C, the chromatographic separation experiment was carried out using a Luna C18 analytical column (150 × 4.6 mm inner diameter, 3 µm particle size, Phenomenex). The mobile phases were formic acid 0.1% in water:ACN 95:5 (v/v; phase A) and ACN (phase B). Using 38% A and 62% B with a flow rate of 1 mL per minute, the column was isocratically eluted. 275 nm was chosen as the ideal wavelength for the RX quantification.

2.6 | Validation of the analytical method

RX and IS singular stock solutions were prepared in MeOH at the concentration of 1000 µg/mL and then diluted to reach a final concentration of 100 µg/mL and stored at −20°C. This last concentration was then diluted to the following concentrations: 10, 5, 2.5, 1, 0.5, 0.1 and 0.05 µg/mL, in order to prepare the calibration curve of RX in plasma. These RX concentrations vs the ratio of IS peak areas were used to create spiked curves. Based on the residual plot, fit test and back calculation, the linearity of the calibration curves in the 0.05–50 µg/mL for plasma range was evaluated. Six plasma samples spiked with IS at high (10 µg/mL), middle (1 µg/mL) and low (0.05 µg/mL) concentration standards were analysed using the same instrument and operator on the same day and three different days, respectively, to determine the intra-day and inter-day precision. These precision values were expressed as the percentage coefficients of variation (CV, %). Comparing the detector responses (in terms of areas) obtained for the extracted quality control samples and those for the pure standards dilutions allowed us to assess the drug recoveries. The recovery was expressed as mean ± standard deviation (SD). The lower limit of quantification (LLOQ) was established as the lowest plasma concentration that produced a signal to noise ratio of 5. The limit of detection (LOD) was estimated as the plasma concentration that produced a signal to noise ratio of 3.

2.7 | Pharmacokinetic and statistical analysis

The data were pharmacokinetically evaluated using a non-compartmental technique (ThothProTMT 4.3; ThothPro LLC). The maximum plasma concentration (C_{max}) and time to attain it (T_{max}) were calculated directly from the concentration vs time curves. The elimination half-life (t1/2λz) was estimated using least squares regression analysis of the concentration-time curve. Using

the linear trapezoidal rule, the area under the concentration/time curve (AUC_{last}) was calculated. Area under the first moment curve (AUMC) was calculated as $\int_0^{\infty} 0\ C(t)dt$. From these values, mean residence time (MRT = AUMC/AUC), and clearance (Cl = dose/AUC) were calculated. The individual value of AUC_{rest} was lower than 20% of $AUC_{(0-\infty)}$, and the square of coefficient of determination (R^2) of the terminal phase regression line was >.85. Values below the LLOQ were not considered for the pharmacokinetic analysis.

The PO and SC bioavailability (F) were calculated using the following equation:

$$F\% = 100 \times \frac{\text{AUC (SC or PO)} \times \text{Dose (IV)}}{\text{AUC (IV)} \times \text{Dose (SC or PO)}}$$

The mean absorption time (MAT) was calculated using the following equation:

$$\text{MAT (PO or SC)} = \text{MRT (PO or SC)} - \text{MRT (IV)}$$

The extraction ratio (E) for RX after IV administration was calculated for goats as the clearance divided by cardiac output, where cardiac output (mL/kg/min) was calculated as body weight (kg) to the power of −0.19 multiplied by 180 (Toutain & Bousquet-Mélou, 2004b).

$$E\% = \frac{\text{Body clearance}}{\text{Cardiac output}} = \frac{\text{Body clearance}}{180 \times \text{Body weight}^{-0.19}}$$

To determine statistically significant differences in pharmacokinetic variables between the three treatment groups, Bonferroni's multiple comparison test (repeated measures ANOVA) was used. The paired t-test was used to compare T_{max}, C_{max}, F% and MAT between the SC and PO groups. A p-value <.05 was considered statistically significant. GraphPad InStat was used for the analyses (GraphPad Software 5.3v).

3 | RESULTS

3.1 | Validation of the method

According to the EMA guidelines, the quantitative HPLC method was fully validated for goats plasma in terms of linearity, intra-day and inter-day precision, selectivity, recovery, LOD and LLOQ (Anonymous, 2012). The method's selectivity was tested for interference with blank plasma and spiked samples, and no peaks interfering with RX were found. With an R^2 of .999 ($y = 0.1681x + 0.0113$), the analytical method demonstrated optimal linearity. The mean extraction recovery was 89% ± 8% and the LOD and LLOQ were 0.01 and 0.05 μg/mL, respectively. A CV% lower than 14.9 and 3.72% was seen for the intra- and inter-day precision, respectively. The mean concentrations for the QCs and LLOQ samples were less than 15% of the nominal values.

3.2 | Animals

The health of the animals was assessed before, throughout, and after the study period by a qualified veterinarian (B L-W). The goats did not show any apparent immediate or delayed (up to 5 days) local or systemic adverse effects.

3.3 | Pharmacokinetics

Figure 1 depicts the semi-logarithmic plot of the mean (±SD) plasma RX concentrations over time after IV, SC and PO administration. RX

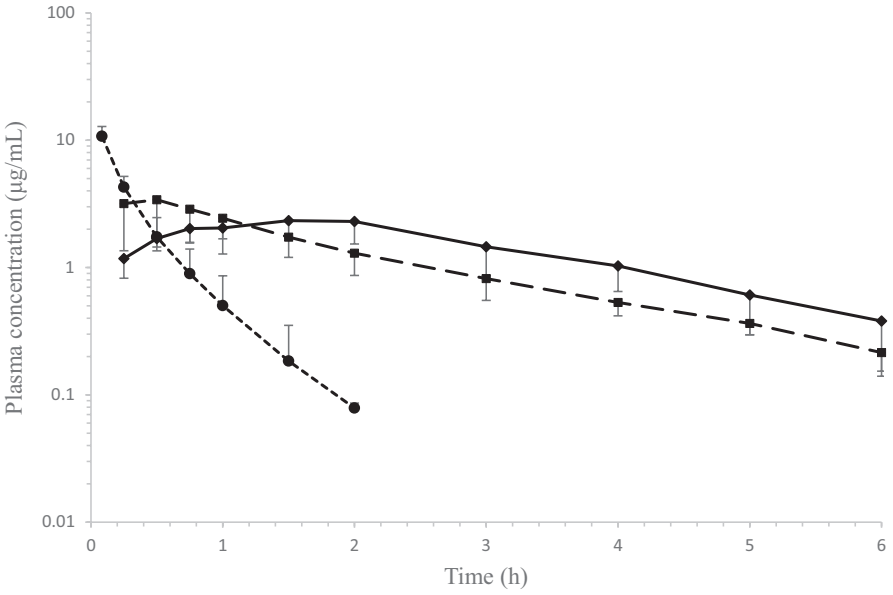

FIGURE 1 Semi-logarithmic mean plasma concentration–time curves of robenacoxib following intravenous (IV, 2 mg/kg, --●--), subcutaneous (SC, 4 mg/kg, —◆—) and oral (PO, 4 mg/kg, --■--) administrations in goats ($n = 8$).

was quantifiable till 2 h IV and 6 h SC and PO. Table 1 displays the mean pharmacokinetic parameters based on non-compartmental pharmacokinetic model. The pharmacokinetic parameters of RX have been presented as geometric means and ranges, except for T_{max} (categorical variable), which was expressed as the median value and range (Julious & Debarnot, 2000). After IV administration, the mean calculated Cl was slow (0.52 L/h/kg), and the V_d was low (0.24 L/kg). As for $AUC_{(0-\infty)}$ corrected for the dose, there was no statistically significant difference between the three routes of administration. The mean bioavailability was determined to be high following SC (98.02%) and PO (91.73%) administration. Extravascular (EV) V_d values corrected for the calculated *F*% were 0.95 L/kg SC and 1.71 L/kg PO and were significantly larger than found in the IV group (0.24 L/kg). The t1/2λz was significantly shorter after IV than after EV administrations (0.32 h IV vs. 1.37 h SC and 1.63 h PO). The MAT_{SC} (2.6 h) and MAT_{PO} (2.01 h) were higher than their respective t1/2λz. These variances may suggest the presence of a flip-flop phenomenon for the extravascular routes. The *E* ratio had an average of 8%.

4 | DISCUSSION

To the best of the authors' knowledge, this is the first study, which reports the pharmacokinetics of RX in goats. The current research aimed to investigate the pharmacokinetics of RX when administered IV, SC and PO. Even though the IV route for RX is not recommended, it was critical to evaluate this route in order to determine true clearance, volume of distribution and absolute bioavailability for the EV administrations. As in Fadel et al. (2022), the IV dose was purposefully chosen lower than for the other routes of administration to reduce potential systemic toxicity and collateral effects. Although dose-independent pharmacokinetics cannot be completely ruled out in goats, RX PK was found to be dose-dependent with linear plasma drug concentrations in dogs (Borer et al., 2017; King et al., 2011; Schmid et al., 2010).

No systemic or local adverse effects were observed following the various routes of administration of RX at a dose of 2–4 mg/kg in goats. It was the case as well in sheep (Fadel et al., 2022), dogs (Jung et al., 2009), cats (King et al., 2013), rabbits (Jeffrey et al., 2023), rats (King et al., 2009) and rainbow trout (Raulic et al., 2021).

Following IV administration in goats, V_d was low (0.24 L/kg) and was comparable to that found in dogs (0.24 L/kg), cats (0.19 L/kg), rats (0.3 L/kg), but higher than that reported in sheep (0.077 L/kg). For NSAIDs generally, the low V_d is associated to the very high plasma protein binding (King et al., 2009; Sakai, 2009). The binding ratio of RX to plasma proteins is unknown in goats and was not assessed in this study. However, at a RX concentration of 2 μg/mL, protein binding exceeded 98% in dogs and cats (Jung et al., 2009). It might be the case in goats as well, but a further study is required to confirm this. The discrepancy in values when compared to sheep might be related to a variation in the degree of plasma protein binding, the presence or absence of an enterohepatic drug cycle, or a difference in body composition. Even though the V_d was low in goats, it remained higher than the average blood volume in these species (0.05–0.06 L/kg). This is consistent with most of the drug remaining in the extra-cellular compartment (Lees et al., 2022). However, earlier studies have reported the selective distribution of RX to sites of inflammation in rats, dogs and cats, with a lengthy residence period

TABLE 1 Mean pharmacokinetic parameters and range of robenacoxib after single IV (2 mg/kg), SC (4 mg/kg) and PO (4 mg/kg) doses in goats ($n=8$).

		IV			SC			PO		
Parameter	**Unit**	**Geo mean**	**Max**	**Min**	**Geo mean**	**Max**	**Min**	**Geo mean**	**Max**	**Min**
$AUC_{(0-t)}$	h×μg/mL	3.78[b,c]	5.97	2.46	7.75	10.09	6.23	6.42	9.88	4.11
$AUC_{(0-\infty)}$ D	h×μg/mL	7.64	12.20	4.96	8.71	11.21	6.41	7.02	10.19	4.58
λz	1/h	2.11[b,c]	3.43	1.32	0.50	0.86	0.25	0.42	0.62	0.31
t1/2λz	h	0.32[b,c]	0.53	0.20	1.37	2.77	0.79	1.63	2.19	1.10
Cl[d]	L/h/kg	0.52	0.80	0.32	0.49	0.69	0.31	0.70	0.15	0.42
Vd[d]	L/kg	0.24[b,c]	0.39	0.17	0.95	2.22	0.51	1.71	4.78	0.67
$MRT_{(0-t)}$	h	0.25[b,c]	0.36	0.21	2.32[a,c]	2.84	1.80	1.81[a,b]	2.13	1.26
$MRT_{(0-\infty)}$	h	0.28[b,c]	0.41	0.22	2.89	5.01	1.96	2.33	3.24	1.46
Cmax	μg/mL	–	–	–	2.34	2.95	1.35	3.34	7.47	2.15
Tmax[m]	h	–	–	–	1.50[c]	2.00	0.75	0.50	0.75	0.25
F	%	–	–	–	98.02	120.46	76.73	91.73	123.00	57.70
MAT	h	–	–	–	2.60	4.60	1.73	2.01	3.00	1.05

Note: [a]Statistically different from IV; [b]Statistically different from SC; [c]Statistically different from PO; [d]Extravascular routes corrected for bioavailability; [m]Median value.

Abbreviations: $AUC_{(0-\infty)}$ D, area under the curve from 0 h to infinity normalized for the dose; $AUC_{(0-t)}$, area under the curve from 0 h to last time collected samples; Cl, plasma clearance; C_{max}, peak plasma concentration; *F*, bioavailability; MAT, mean absorption time; $MRT_{(0-\infty)}$, mean residence time from 0 h to infinity; $MRT_{(0-t)}$, mean residence time from 0 h to last time collected samples; t1/2λz, terminal half-life; T_{max}, time of peak concentration; V_d, volume of distribution; λz, terminal phase rate constant.

in exudates (>24 h) and a long duration of activity (King et al., 2009; Pelligand et al., 2012, 2014).

In this study, the Cl value following IV administration of RX was low (0.52 L/h/kg), comparable to that found in cats (0.44 L/kg/h; King et al., 2013), lower than that found in dogs (moderate; 0.81 L/kg/h; Schmid et al., 2010), and substantially higher than that found in sheep (0.056 L/h/kg) and rats (0.14 L/h/kg). Species differences in the isoform composition, expression and activities of biotransformation enzymes and the functions of excretory organs (Dantzler, 2016) may be the main reasons behind the differences in Cl of RX in the different animal species. Additionally, the different cardiac output among species can account to the species differences (Toutain & Bousquet-Mélou, 2004b). Indeed, the estimated *E* for RX found in the present study (8%) was similar to that found in cats and dogs, for which the range was between 5% and 15% (King & Jung, 2021; Toutain & Bousquet-Mélou, 2004b). In sheep, however, *E* was considerably lower (1%). Because of their feeding behaviour and superior capacity to detoxify exogenous compounds, goats have a more active metabolism and a higher elimination capacity than sheep (Aksit et al., 2015; Wells, 2010), as evidenced in numerous studies (Aksit et al., 2015; Bogan et al., 1987; Gokbulut et al., 2009, 2011, 2014; Hennessy et al., 1993). Nonetheless, knowing that RX is extensively metabolized by the liver in cats and dogs (EMA, 2018), it may be presumed that the higher rate of hepatic metabolism and a higher hepatic extraction ratio in goats resulted in the faster clearance of RX than in sheep.

The EV routes exhibited a 4-fold higher t1/2λz than IV (1.37 h SC; 1.63 h PO; 0.32 h IV), suggesting the occurrence of a flip-flop phenomenon. This can occur when drugs have a formulation with poor solubility, such as RX (Zornoza et al., 2006). If MAT is significantly longer than MRT_{IV}, as it was in our case, this would confirm a flip-flop situation (Toutain & Bousquet-Mélou, 2004a). This is supported by the visual comparison of the terminal phase of the EV curves (λz) in Figure 1, which are substantially lower than those of the IV plasma level (EV curves have a flatter decline), exhibiting significantly statistical differences ($p < .0001$; Table 1; Winter et al., 2022; Zornoza et al., 2006). However, as reported in the results, the significant difference in V_d values between IV and EV routes might have also triggered the t1/2λz difference. This inter-occasion variability in V_d for the same individuals can be caused by a variety of factors and was previously evidenced in several studies. First, due to technical circumstances, the washout interval between the IV and EV phases was four months. This period is lengthy, especially in the case of 5-month-old goats that are constantly growing and consequently undergoing physiological changes (higher fat proportion with age, digestive tract development, hemodynamic factors; Bregante et al., 2000; Lüders et al., 2010; Waxman et al., 2004). Second, the environmental changes might have influenced the values as well. There was a significant environmental temperature difference between the first phase (held in August at 35°C) and the second and third phases (held in December at −15°C). Large temperature differences have been reported to affect the pharmacokinetics and pharmacodynamics of a drug (Johansson, 2001). To note, the t1/2λz of RX in goats (0.32 h) following IV treatment was significantly lower than in sheep (2.64 h). This lower t1/2λz might have been attributed to either a smaller distribution volume, which is not the case, or to faster clearance, which explains the situation as previously indicated.

The *F* values observed in this study were high (98.02% SC and 91.73% PO), above those of sheep (46% SC and 17% PO), dogs (88% SC and 84% PO) and cats (69% SC and 49% PO). This disparity between the values is thought to be due to species-specific differences (Toutain et al., 2010).

For practical reasons, the washout period was also extended. It had limitations, particularly because it was established as a parallel research rather than a cross-over study, which would have reduced intra- and inter-individual variability. Another limitation of this study is that no pharmacodynamic study was conducted.

In conclusion, the findings related to IV administration route suggest that RX might not be a suitable drug for use in goats due to its short half-life. However, the SC and PO routes appear to be convenient for the drug's occasional use. Despite the low t1/2λz in other species as well, the reported prolonged duration of effect of RX in peripheral tissues provides plausibility to its application once per day, nonetheless additional research is warranted.

AUTHOR CONTRIBUTIONS

Although Charbel Fadel was the primary planner and organizer of the experiment stages, each author's contribution to the piece was essential since they meticulously integrated the experiment's findings. All the authors participated as well in each step of the research process.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest in publishing this work.

DATA AVAILABILITY STATEMENT

The data sets used and/or analysed during the current study are available from the corresponding author, upon reasonable request.

ANIMAL WELFARE AND ETHICS STATEMENT

The animal experiment was approved by the Lebanese ministry of Agriculture ethical committee, verifying that this study complies with European standards for animal welfare guidelines (study protocol number 1120221).

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