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ORIGINAL ARTICLE

Disposition kinetics of robenacoxib following intravenous and oral administration in geese (*Anser anser domesticus*)

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Abstract

Robenacoxib (RX) is a veterinary cyclooxygenase-2 selective inhibitor drug. It has never been tested on birds and is only labelled for use in cats and dogs. The purpose of this study was to assess its pharmacokinetics in geese after single intravenous (IV) and oral (PO) administrations. Four-month healthy female geese ($n = 8$) were used. Geese were subjected to a two-phase, single-dose (2 mg/kg IV, 4 mg/kg PO), open, longitudinal study design with a four-month washout period between the IV and the PO phases. Blood was collected from the left wing vein to heparinized 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 an UV 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 0.35 h, 0.34 L/kg, and 0.68 L/h/kg, respectively. For the PO route, the mean peak plasma concentration was 6.78 μg/mL at 0.50 h. The $t1/2\lambda z$ was very short and significantly different between the IV and PO administrations (0.35 h IV vs. 0.99 h PO), suggesting the occurrence of a flip-flop phenomenon. The Cl values corrected for the *F*% were significantly different between IV and PO administrations. It might have been a consequence of the longitudinal study design and the altered physiological and environmental conditions after a 4-month washout period. The absolute oral *F*% computed with the AUC method surpassed 150%, but after normalizing it to $t1/2\lambda z$, it was 46%. In conclusion, the administration of RX might not be suitable for geese, due to its short $t1/2\lambda z$.

KEYWORDS
coxib, geese, non-steroidal anti-inflammatory, pain management, pharmacokinetics, robenacoxib

1 | INTRODUCTION

One of the largest food industries in the world is the avian industry, particularly the poultry industry. Even though geese are some of the earliest domesticated birds raised for commercial purposes, they are regarded as minor species because they are not as frequently produced as other avian species such as chickens and turkeys (Cilavdaroglu et al., 2020; Kozák et al., 2010). However, geese production has expanded worldwide in the recent years due to rising demand, particularly in China, Hungary, Ukraine, Egypt, and Poland (Cilavdaroglu et al., 2020; Kozák et al., 2010). This is because they, among the birds' species, have the highest growth intensity and capacity for utilizing green forages (Romanov, 1999). They are bred for high-value products like meat, fatty liver, eggs, and feathers (Hugo, 1995; Romanov, 1999). They also aid in weed and pest control, which makes them useful for integrated farming (Hugo, 1995).

Avian pain management is characterized by multiple challenges. Recognizing pain and assessing its intensity are both essential for effective management. Behaviour associated with painful stimuli is often subtle and not very specific in birds. Thus, the farmer's appreciation of the intensity of pain, as well as his familiarity with the normal behaviour of both animal species and individual birds in order to recognize signs of pain, is critical for the selection of an analgesic drug and its dosage regimen (Hawkins, 2006). According to numerous studies (McGeown et al., 1999; Proudfoot & Hulan, 1983; Shlosberg et al., 1996; Thomas et al., 1966), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are effective for a wide range of clinical treatments in avian medicine and are used to reduce pain and inflammation of various origins, including musculoskeletal, visceral and postoperative pain. Arthritis and degenerative joint disease are two of the most serious illnesses affecting waterfowl, particularly young geese (Degernes et al., 2011).

The drug's pharmacokinetic (PK) processes, differ significantly between mammals and birds, as well as between different avian species. Some NSAIDs exhibit significant species differences in their primary PK properties, demonstrating that it is difficult to extrapolate PK data and posology from mammals to birds and between different bird species. Furthermore, different animal species, including birds, may have very different NSAID safety profiles (Baert & De Backer, 2003; Hawkins, 2006).

Various NSAIDs, like meloxicam, piroxicam, carprofen, ketoprofen, celecoxib and mavacoxib, have been used in birds to treat pain and inflammation (Dhondt et al., 2017). However, their usage is extra-label. The gastrointestinal, renal, and haematopoietic systems are all affected by the toxic effects of this class of medications. Nephrotoxicity is the most frequently reported NSAID side effect in birds (Jayakumar et al., 2010; Pereira & Werther, 2007; Zollinger et al., 2011). For instance, in some countries, the vulture population has decreased recently, due to NSAIDs such as diclofenac and flunixin, which cause kidney failure due to renal residues (Toutain et al., 2010; Zorrilla et al., 2015). Yet, the safety of tolfenamic acid and meloxicam has been demonstrated in vultures and is most probably due to their cyclooxygenase (COX)-2 selectivity (Turk et al., 2021). In this case, coxibs might be an even safer option for application in avian species due to their higher COX-2 selectivity and efficacy compared to the previously stated drugs (Flower, 2003; Kamata et al., 2012).

Robenacoxib (RX) is a highly selective COX-2 inhibitor, approved for use in cats and dogs to treat musculoskeletal and post-operative pain and inflammation. Its pre-clinical safety studies indicated that it produces minimal adverse effects, whether renal or gastrointestinal, even at very high dosages, in healthy rats, dogs and cats (Lees et al., 2022). As RX has a great safety profile in other species and because NSAIDs' PK data in geese is limited or extrapolated from other species, the goal of this study was to assess the PK of RX following single oral (PO) and intravenous (IV) administration.

2 | MATERIALS AND METHODS

2.1 | Chemicals and reagents

The sodium chloride (NaCl) and pure powders of RX and diclofenac used as the internal standard (IS) with a standard purity of 99.0% were purchased from Sigma-Aldrich (Milan, Italy). Acetonitrile (ACN), methanol (MeOH), and formic acid were purchased from VWR chemicals (Oud-Heverlee, Belgium) in high-performance liquid chromatography (HPLC) grade. With the aid of a Milli-Q Millipore Water System, deionized water was produced (Millipore, Darmstadt, Germany). The aqueous and organic components of the mobile phase were degassed under pressure and combined in the HPLC system. The mobile phases were filtered through 0.2 μm cellulose acetate membrane filters using a solvent filtration apparatus (Sartorius Stedim Biotech, Goettingen, Germany).

2.2 | Animals and experimental design

This study included eight 4-month-old female geese chosen randomly from a larger group. Based on serum chemistry, physical examination, and haematological analyses, they were deemed in good health and acclimatized for 1 week in a 60 m^2 enclosure with an indoor shelter of 9 m^2 prior to the start of the study. The geese were fed a drug-free pelleted diet twice a day, and water was provided ad libitum. The daily behaviour and appetite of the geese were observed. The animal experiment was approved by the Lebanese ministry of Agriculture ethical committee, verifying that this study complies with appropriate regulations and animal welfare international guidelines (study protocol number 1120222).

A two-phase, two-dose (2 mg/kg IV, 4 mg/kg PO), open, longitudinal study design with a washout period of 4 months was carried out. In the first phase (September 2022), eight geese (four-month-old) were administered intravenously with 2 mg/kg RX (Onsior®, 20 mg/mL) using a sterile 20-gauge 3.75 cm needle in the left-wing vein. In this period, the geese body weights (BW) ranged between 3.40 and 4.30 kg with an average of 3.72 kg. In the second phase

(December 2022), geese were administered orally with 4 mg/kg RX (Onsior®, 20 mg/tablet) via crop gavage by a rounded tip metal catheter. The RX tablets were carefully grinded then weighed and partitioned to form the 4 mg/kg PO doses, then the catheter was promptly flushed with 5 mL of water. The BWs of the animals ranged between 4.55 and 5.43 kg with an average of 5.10 kg. Blood (approximately 2 mL) was collected from the right-wing vein by direct venipuncture at 0, 0.085 (for IV only), 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, and 24 h. Blood was collected in heparinized tubes and centrifuged at 1500 x *g*. The harvested plasma was stored at −20°C and analysed within 10 days of collection.

2.3 | Sample extraction

The sample preparation method was determined using a previously published method (Jung et al., 2009), and modified as in Fadel et al. (2022). To boost water's ionic power, 50 mg of NaCl was mixed into 200 µL of plasma. After that, the plasma was spiked with 50 µL of an IS solution in MeOH (50 µg/mL). Then 800 mL of ACN was added. After vigorous vortex mixing (30 s), the samples were shaken at 60 oscillations per min, for 10 min, before being centrifuged at 4000*g* for 10 min. The upper layer was transferred to a clean tube and gently steamed with nitrogen while drying at 45°C. The residue was dissolved in 120 µL of ACN:H_2O 60:40 (v/v), vortexed for 1 min, 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.

2.4 | HPLC instrumentation and analytical conditions

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

2.5 | Validation of the analytical method

RX and IS singular stock solutions were prepared in MeOH at 1000 µg/mL concentration, then diluted to a final concentration of 100 µg/mL and stored at −20°C. This final 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. Spiked curves were created using these RX concentrations vs the ratio of IS peak areas. The linearity of the calibration curves in the range of 0.05–50 µg/mL for plasma was evaluated using the residual plot, fit test, and back calculation. 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 %). We were able to assess drug recoveries by comparing the detector responses (in terms of areas) for the extracted quality control samples and those for the pure standards dilutions. The recovery was calculated using the mean and 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 (EMA, 2008).

2.6 | Pharmacokinetics and statistical analysis

Using a non-compartmental method, the pharmacokinetic evaluation of the data was performed (ThothPro™ 4.3; ThothPro LLC, Poland). The concentration vs time curves were used to directly calculate the maximum plasma concentration (C_{max}) and the time required to reach it (T_{max}). By analysing the concentration–time curve using least squares regression, the elimination half-life ($t1/2\lambda z$) was calculated. The area under the curve (AUC) was calculated by linear log trapezoidal for the IV administration and by the linear-up log-down rule for the oral administration. Area under the first moment curve (AUMC) was calculated as $\int_0^\infty 0C(t)dt$. 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 >0.85. Values below the LLOQ were not considered for the pharmacokinetic analysis.

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

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

For random inter-occasion clearance variability, the formula was corrected by the terminal half-life (Wagner, 1967) using the following equation:

$$F\% = 100 \times \frac{\text{AUC (PO)} \times t1/2\lambda z\text{(IV)}}{\text{AUV (IV)} \times t1/2\lambda z\text{(PO)}}$$

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

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

The body extraction ratio (E_{body}) for RX after IV administration was calculated using Cl/CO (Toutain & Bousquet-Mélou, 2004b), where CO (mL/kg/min) was the cardiac output calculated according to the allometric equation in birds: 290.7 × body weight (in kg)$^{0.69}$ (Grubb, 1983; Waxman et al., 2019).

To determine statistically significant differences in pharmacokinetic variables between the two treatment groups, the paired *t*-test was used. A *p*-value <.05 was considered statistically significant. GraphPad InStat was used for the analyses (GraphPad Software 5.3v).

3 | RESULTS

3.1 | Analytical method validation

The analytical method showed an optimal linearity (R^2 = 0.99; $y = 0.1817x + 0.0121$) in the range of 0.05–50 μg/mL. The recovery was seen to be 87 ± 8.2%. The LOD and LLOQ were 0.01 and 0.05 μg/mL, respectively. A CV% lower than 13.8 and 3.19% was seen for the intra- and inter- day precision, respectively. The mean concentrations for the QCs and LLOQ samples were <15% of the nominal values.

3.2 | Animals

The health of the geese was assessed before, throughout, and after the study period by a qualified veterinarian (B L-W). The geese did not show any apparent immediate or delayed (up to 7 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 single IV and PO administration. RX was quantifiable till 1.5 h IV and 6 h PO. Table 1 displays the mean pharmacokinetic parameters based on non-compartmental pharmacokinetic model. Apart from T_{max} (a categorical variable), which was expressed as the median value and range, the PK parameters of RX have been presented as geometric means and ranges (Julious & Debarnot, 2000). After IV administration, the mean Cl value was moderate (0.68 L/h/kg), and the V_d value was low (0.34 mL/kg). Peak RX plasma concentration (C_{max} = 6.78 μg/mL) was achieved rapidly (T_{max} = 0.5 h). The oral Cl (0.14 L/h/kg), corrected for *F*%, was significantly lower than that IV (0.68 L/h/kg). Oral bioavailability assessed using the AUC calculation exceeded 150%, while it was 46.44% using the $t1/2\lambda z$ corrected formula. Additionally, MAT_{PO} (1.45 h) was higher than the oral $t1/2\lambda z$ (0.99 h), and the $MRT_{(0-\infty)}$ for PO (1.86 h) was significantly higher than that of IV (0.37 h), suggesting the presence of a flip-flop phenomenon. The E_{body} was low with a geometric mean of 1%.

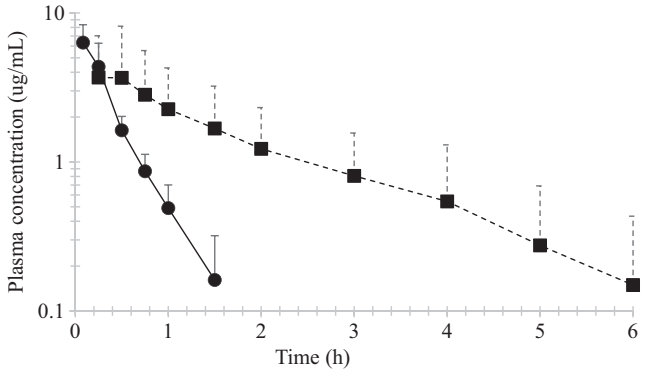

FIGURE 1 Semi logarithmic mean (±SD) plasma concentration–time curves of robenacoxib, following intravenous (IV, 2 mg/kg, —●—) and oral (PO, 4 mg/kg, --■--) administration in geese (n = 8).

4 | DISCUSSION

To the best of the author's knowledge, there have been no previous RX studies in geese. No systemic or local adverse effects were observed following IV and PO administrations at a dose of 2–4 mg/kg in geese, as it was the case in sheep (Fadel et al., 2022), goats (Fadel et al., 2023), dogs (Jung et al., 2009), cats (King et al., 2013), rabbits (Jeffrey et al., 2023), rats (King et al., 2009), and rainbow trouts (Raulic et al., 2021).

In avian species, drugs can be provided individually or as flock therapy, with drinking water and feed medication being the most used techniques. In this study, however, drinking water and feed medicine techniques were not recommended due to the various limitations, including differences in drug intake across geese, imprecise dosing, and solubility difficulties (Powers, 2006; Turk et al., 2021; Vermeulen et al., 2002). While parenteral medication is an alternative form of delivery for the quickest onset of action in critically ill birds, oral gavage offers accurate dosing and no stability issues (Flammer, 1994; Powers, 2006; Vermeulen et al., 2002). Although the IV route for RX is not recommended, it was critical in this study in order to determine the true Cl, V_d, and the absolute *F*% for the oral route. To avoid systemic toxicity and side effects, the IV dose was purposely set lower than that PO (Borer et al., 2017; King et al., 2011; Schmid et al., 2010). Still, the dosages for both administrations were within the therapeutic ranges recommended for cats and dogs (EMA, 2008).

Following IV administration, V_d was low (0.34 L/kg), and was comparable to that in dogs (0.24 L/kg), cats (0.19 L/kg), goats (0.24 L/kg), rats (0.3 L/kg), and higher than that in sheep (0.077 L/kg). Generally, NSAIDs are characterized by a small volume of distribution, due to the high binding to serum albumin. Indeed, RX (2 μg/mL) protein binding exceeded 98% in dogs and cats (Jung et al., 2009). Given the similar V_d, it may be the case as well in geese. Inopportunely, plasma protein binding was not assessed in this study. The discrepancies in V_d values between geese and sheep may be explained by differences in body temperature and body components (fat/water partition) (Dorrestein, 1991; Toutain et al., 2010), albeit the precise reasons are yet unclear.

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

		IV			PO		
Parameter	Unit	Geo mean	Max	Min	Geo mean	Max	Min
$AUC_{(0-t)}$	h*µg/mL	2.8*	3.86	1.89	12.12	25.93	3.92
$AUC_{(0-\infty)}$ D	h*µg/mL	5.85*	8.22	4.14	12.6	27.62	4.5
λz	1/h	1.96*	2.63	0.89	0.74	1.163	0.44
$t1/2\lambda z$	h	0.35*	0.77	0.26	0.99	1.55	0.75
Cl[c]	L/h/kg	0.68*	0.96	0.48	0.14	0.11	0.41
V_d[c]	L/kg	0.34	0.59	0.21	0.19	0.26	0.03
$MRT_{(0-t)}$	h	0.3*	0.45	0.18	1.66	1.86	1.41
$MRT_{(0-\infty)}$	h	0.37*	0.71	0.28	1.86	2.46	1.54
C_{max}	µg/mL	_	_	_	6.78	15.94	2.23
T_{max}[m]	h	_	_	_	0.5	1	0.25
F	%	_	_	_	46.44	133.72	21.1
MAT	h	_	_	_	1.45	2.13	1.01

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

Cl following IV administration of RX in geese was moderate (0.68 L/h/kg), and was higher than that found in sheep (0.056 L/h/kg; Fadel et al., 2022), rats (0.14 L/h/kg; King et al., 2009), and slightly higher than in cats (0.44 L/h/kg; King et al., 2013), and goats (0.52 L/h/kg; Fadel et al., 2023). Differences in Cl of RX in different animal species may be due to species disparities in isoform composition, expression, and activities of biotransformation enzymes, as well as excretory organ functions (Dantzler, 2016). Birds are generally known to have a faster clearance than larger-sized mammals; this is due to their higher rate-specific metabolic rate. They have larger excretory organs than large mammals, in relation to their size (Frazier et al., 1995). However, E_{body} in geese was low (1%). This might indicate that geese have a low ability to eliminate RX (Toutain & Bousquet-Mélou, 2004b). RX is extensively metabolized by the liver in cats and dogs (EMA, 2008). This may not be the case in geese. Even though the biotransformation enzymes are ubiquitous in avian species, little is known about their function, and excretory organs in birds differ physiologically and anatomically from those in mammals (Dorrestein, 1991; Toutain et al., 2010; Vermeulen et al., 2002). Thus, further investigations are warranted on this subject.

Regarding $t1/2\lambda z$, it was significantly longer (0.99 h) for the oral than the IV route (0.35 h). This might be due to a flip–flop phenomenon. It may occur in formulations with poor solubility, such as RX (Zornoza et al., 2006), and it can be confirmed by having a MAT longer than the MRT_{IV} (Yáñez et al., 2011; 1.45 h > 0.37 h). Given the short T_{max} in previous studies (0.25–1.5 h), and in this study (0.5 h), this phenomenon was suggested to have occurred as well in cats, dogs, and rats (Lees et al., 2022). Another main reason that could directly impact the $t1/2\lambda z$ is the Cl, which was actually significantly different between the IV and PO routes for the same individuals. This inter-individual variability may be due to the long washout interval period (4 months), because of technical constraints. This period is vast, particularly in the case of four-month-old geese, which are continuously growing and, as a result, undergoing physiological changes. In fact, growth-dependent decrease in drug elimination has been frequently described in bird species (Fadel & Giorgi, 2023; Poźniak et al., 2020a, 2020b; Santos et al., 1996; Świtała et al., 2016), attributed mainly to changes in hemodynamics, metabolism, and drug binding. The $t1/2\lambda z$ in this study after IV administration (0.35 h) was similar to that in goats (0.32 h) and lower than that in dogs (0.69 h), cats (1.49 h), sheep (2.64 h), and rats (1.9 h). It is known that $t1/2\lambda z$ for many NSAIDs varies significantly between species (Hawkins, 2006). Indeed, as for meloxicam, celecoxib, and mavacoxib, previous research demonstrated that dose extrapolation is not a suitable method for dose and posology determination in avian species, due to inter-species differences in PK values (Baert & De Backer, 2003; Dhondt et al., 2017).

When F% was calculated using the classical equation, the values were abnormal and exceeded 150%. Indeed, when determining the absolute bioavailability, the error can be major if the two concentration curves (IV and PO) correspond to different clearances (Rescigno, 2000). It is because AUC is proportional to the fraction absorbed only if the clearance is constant and the concentration is uniform; in other cases, F% cannot be determined by only comparing the AUCs (Rescigno, 2000). For such random inter-occasion Cl variability, it has been suggested to correct the computed F% by $t1/2\lambda z$ (Toutain & Bousquet-Mélou, 2004a; Wagner, 1967). Hence, the oral F resulted as moderate (46%), similar to that in cats (49%), substantially higher than that in sheep (16%), and lower than that in dogs (62–84%) and rats (80%). Anatomic and physiological differences in

the digestive tract, as well as levels of efflux proteins that contribute to intestinal barrier function, might account for this difference, as do species-specific differences (Turk et al., 2021). The T_{max} of 0.5 h was comparable to that of other species. At first sight, it appears to indicate rapid absorption; however, as previously indicated, this short T_{max} might be more likely due to flip-flop PK (Lees et al., 2022).

This study accounts for some limitations. First, the washout period was very long for practical/technical reasons. It endured limitations, particularly because the study was designed as longitudinal rather than as a cross-over study due to technical constraints, which would have reduced intra- and inter-individual variability. Second, the absence of a pharmacodynamic investigation is another drawback of the study. Assessing the IC_{80} for COX-2 inhibition would be vigorous to assess RX plasma concentrations in geese that could provide appropriate analgesia and anti-inflammatory effects (Warner et al., 1999).

From the pharmacokinetic side, RX, due to its brief terminal half-life, might not be suitable for use in geese. However, in other animal species where RX had short *t*1/2*z* values similar to geese, the therapeutic effects of RX lasted up to 24 h (King et al., 2009; Pelligand et al., 2014). Further studies are warranted to clarify this issue.

AUTHOR CONTRIBUTIONS

Despite Charbel Fadel's role as the primary planner and organizer of the experiment stages, the contribution of each author to the piece was crucial due to their meticulous integration of the experiment's findings. Furthermore, all the authors actively participated in every 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 held in Lebanon and was approved by the Lebanese ministry of Agriculture ethical committee, verifying that this study complies with international standards for animal welfare guidelines (study protocol number 1120222).

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