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Meloxicam blood levels are not affected by sex-related hormones in male and female goats

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Abstract: The present study aims to investigate the interaction between the non-steroidal anti-inflammatory (NSAID) drug meloxicam and sex hormones in seasonal polyoestrous male and female Saanen goats. It was hypothesised that sex hormones, both steroidal and peptide hormones, may influence the serum concentration of the lipophilic drug meloxicam. In the study, the relationship between plasma meloxicam concentration (µg/ml) and the levels of follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), testosterone, oestradiol (E2), and progesterone (P4) was evaluated. For this purpose, six male and six female Saanen goats aged one year were intravenously administered a 0.5 mg/kg dose of meloxicam, and blood samples were collected at different time points (0, 5, 30 min, and 2, 8, 24, 48 h) to obtain plasma and serum. The hormone levels were determined by ELISA, following the manufacturer's instructions, and drug concentrations were measured by HPLC-UV. While the study found no direct correlation between the meloxicam levels and the sex hormones, significant sex-related differences in the hormone levels underscore the importance of considering sex-related physiological differences in veterinary pharmacology. These results will establish a scientific basis for future research on species- and sex-specific dosage adjustments.

Keywords: NSAIDs; reproductive hormones; Saanen goats

Goats play a significant economic role in many regions and are raised within diverse production systems. Local communities can increase livestock productivity across diverse climatic conditions by adapting to challenging environmental factors, such as enhanced resilience to heat stress, drought, and humidity, as well as improved pasture intake and digestibility (Delgadillo et al. 1997; Fatet et al. 2011). Products derived from goats include meat, milk, fibre, and leather. Goat milk and meat

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can be exported and are also widely consumed locally. In developed countries, goat milk and dairy products, especially cheese, are extensively consumed and commercially marketed. Dairy products and milk are significant contributors to human nutrition (Haenlein 2004; Devendra 2010).

Goats exhibit seasonal variation in their reproductive activity in response to changes in the annual photoperiod. Factors such as the latitude, climate, food availability, breed, and breeding system all influence the initiation and duration of their reproductive cycles throughout the year (Fatet et al. 2011). In female goats, ovulation occurs spontaneously during the final stages of oestrus (Greyling 2010). The ovarian cycle consists of two phases: the follicular phase and the luteal phase. The follicular phase involves the maturation of gonadotropin-dependent follicles and culminates in the formation of the ovulatory follicle. The follicle-stimulating hormone (FSH), released by the pituitary gland, promotes the growth of these follicles during the follicular phase. The proestrus refers to the initial phase of the follicular cycle, which occurs before visible signs of oestrus behaviour appear. The period during which the oestrus behaviour is evident and continues until ovulation is known as the oestrus phase. Ovulation marks the beginning of the luteal phase. In this phase, the cells of the ovulating follicle transform into luteal cells, forming the corpus luteum. These luteal cells release progesterone (P4) (Fatet et al. 2011).

In goats, the plasma P4 levels correlate with the corpus luteum status (Orita et al. 2000). During the luteal phase, progesterone suppresses ovulation, but gonadotropin-dependent follicular development continues in a wavelike manner. As the luteal phase progresses, the progesterone secretion decreases, and the corpus luteum undergoes regression (luteolysis) due to the release of prostaglandin F2α from the non-pregnant uterus. A new follicular phase begins when the gradual decline in plasma progesterone levels lifts the inhibition of gonadotropic hormone release (Fatet et al. 2011). Testosterone, the primary androgen produced by Leydig cells, has both anabolic and androgenic effects. The anabolic effects stimulate the growth of non-reproductive organs, such as the liver, kidneys, and muscles. In contrast, the androgenic effects focus on stimulating and maintaining the male reproductive system. Additionally, testosterone enhances the lipid metabolism and plays a significant role in regulating the oxidative phase of glucose metabolism (Gupta et al. 2008; Gofur et al. 2014).

The gonads are the only organs that produce anti-Müllerian hormone (AMH), a 140-kDa glycoprotein dimer belonging to the transforming growth factor (TGF)-β family (Monniaux et al. 2012). AMH plays an important role not only in male sex differentiation, but also in female reproduction. In females, this hormone is secreted by the granulosa cells in developing ovarian follicles and is essential for folliculogenesis (Hayes et al. 2016). Male goats are seasonal breeders, with their reproductive activity primarily triggered by changes in daylight. At temperate latitudes, plasma testosterone levels are very low from January to May and increase significantly from July to November in Mediterranean goats (Todini et al. 2007).

Hormonal responses regulate the utilisation of serum proteins in muscle protein synthesis. In most animals, testosterone and oestrogens have anabolic effects (Eckersall 2008). Emphasising the sex differences can clarify the fundamental, modifiable causes of diseases and highlight significant findings related to the optimal therapeutic efficacy and toxicity (Madla et al. 2021). Sex-related changes in bioavailability can vary depending on the medication's route of administration, and the physiological differences in the absorption organs. Additionally, variations in the drug metabolism and transport mechanisms occur during the drug's initial passage through the intestine or liver (Schwartz 2003; Bakhti-Suroosh et al. 2021; Mauvais-Jarvis et al. 2021). Understanding gender differences in pharmacokinetics and pharmacodynamics is crucial for achieving reliable and effective therapeutic drug concentrations (Soldin and Mattison 2009).

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in veterinary medicine to treat various conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and postoperative pain, including post-castration pain (Luger et al. 1996; Weeder et al. 2024). Goats are particularly sensitive to pain and may even experience sudden death if pain is not properly managed after surgical procedures (Galatos 2011). However, no NSAID products are currently approved for use in sheep and goats (Smith et al. 2021). Meloxicam is a lipophilic NSAID belonging to the oxicam class. It preferentially inhibits COX-2 over COX-1, resulting in fewer adverse effects than non-selective NSAIDs (Del Tacca et al. 2002; Ahmadi et al. 2022).

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Meloxicam is commonly used off-label for pain management in sheep and goats.

Research has shown that NSAIDs can inhibit testosterone glucuronidation via hepatic UDP-glucuronosyltransferase (UGT) enzymes and may also interact with the androgen metabolism through the UGT pathway (Sten et al. 2009; Joo et al. 2015). However, the possible modulation of meloxicam concentrations by endogenous sex hormones has not yet been investigated in goats. The present study aimed to evaluate the relationship between the plasma meloxicam concentrations and circulating sex hormone levels at multiple time points after the intravenous administration in male and female goats. It was hypothesised that both steroidal and peptide hormones, which are involved in metabolic processes, may influence the serum concentration of the lipophilic drug meloxicam. Understanding whether hormonal variations contribute to inter-sex differences in plasma drug levels could provide a basis for future studies focusing on sex-specific pharmacological responses and optimal therapeutic regimens in small ruminants.

MATERIAL AND METHODS

Animals

The trial was carried out on one-year-old female (n = 6) and male (n = 6) Saanen breed goats raised at Cukurova University Faculty of Agriculture Research and Application Farm. The female goats weighed 25–32 kg on average, whereas the male goats weighed 32–41 kg on average. The female goats had not been previously bred and were not in oestrus. No medication was administered in the two months preceding the experiment. All the protocols on the animals were approved (Approval Code: 7-1, Approval Date: 25.07.2024) by the Ethics Committee of the Cukurova University, Health Sciences Experimental Application and Research Centre. Experiments involving both male and female subjects were conducted concurrently in late autumn, a timeframe selected to coincide with males' rising endogenous testosterone levels. Plasma and serum samples were obtained from the blood using the infrastructure at Cukurova University, Ceyhan Veterinary Faculty, and stored at –20 °C until the end of the study.

Experimental plan

The goats were administered a single dose of meloxicam at 0.5 mg/kg via intravenous injection. Blood samples were collected from the *vena jugularis* at 0 (control) and 5, 30 min, 2, 8, 24, 48 h following the administration of the drug, in 3 ml separator gel tubes without an anticoagulant for the hormone analysis, and in heparinised tubes for the plasma drug concentration. The plasma and serum samples were stored at –20 °C until analysis.

Determination of the meloxicam level in plasma

The plasma concentrations of meloxicam were determined by high-performance liquid chromatography (HPLC) with a photodiode-array (PDA) detector. Chromatographic analyses were conducted with an Agilent 1260 HPLC system (Agilent, Waldbronn, Germany).

An analytical column (Eclipse XDB-C18, 5 µm, 250 mm × 4.6 mm; Agilent, Waldbronn, Germany) was used, along with a Nucleosil C18 guard column (Phenomenex, Macclesfield, UK), maintained at 50 °C in a column oven (G1316A) during the analysis.

The mobile phase comprised ultra-pure water (H_2O), methanol, and acetonitrile in a 40 : 30 : 30 (v/v/v) ratio, with the pH adjusted to 3.5 using phosphoric acid. This mobile phase was delivered isocratically at a flow rate of 1 ml/min.

A photodiode-array detector (G4212B) was set to 355 nm. Throughout the study, a constant volume of 50 µl was used for each injection.

The plasma samples were analysed using chromatography, with each individual analysis taking 9 minutes

Stock analytical standard solutions of meloxicam (100 µg/ml) and the internal standard, piroxicam (5 µg/ml), were prepared in a mixture of acetonitrile and ultra-pure water. These solutions were stored in glass bottles at 4 °C. The meloxicam stock solution was then diluted with an acetonitrile-ultrapure water mixture to create intermediate standard solutions at concentrations of 0.1, 0.5, 1, 5, 10, and 50 µg/ml, which were used togenerate the desired plasma spike concentrations.

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Plasma extraction procedure

The plasma concentrations of meloxicam were determined by HPLC with a diode-array detector, following the liquid-liquid phase extraction procedures described by Karademir et al. (2016), with some minor modifications outlined below.

In this procedure, blank plasma samples (0.25 ml) were spiked with 25 µl of a meloxicam standard solution to achieve final concentrations of 0, 0.01, 0.05, 0.1, 0.5, 1, 5, and 10 µg/ml. The plasma samples, both spiked and experimental, were combined with 50 µl of an internal standard (piroxicam at 5 µg/ml). Following this, 0.1 g of magnesium sulphate heptahydrate was added, and vortexed for one minute. Next, 1 ml of acetonitrile was added to deproteinise the plasma samples, and the mixture was vortexed again for one minute, then centrifuged at 13 684 *g* for 5 minutes. The upper organic phase was carefully transferred to a 10 ml glass tube and evaporated in a vacuum concentrator at 50 °C. The completely dried residue was then dissolved in 200 µl of the mobile phase and vortexed for 15 seconds. Finally, a 50 µl aliquot of this solution was injected into the HPLC system for analysis.

Validation of the analytical method

The analytical method validation for meloxicam in plasma was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (ICH 2005). Recoveries were assessed by comparing the peak areas from the spiked plasma samples to the direct injections of the standards in the mobile phase. The inter- and intra-assay precision was evaluated with the drug-free goat plasma samples processed on different days. The calibration graph ranged from 0.01 to 10 µg/ml. The slope of the peak area versus the concentration was determined by least-squares linear regression, and the correlation coefficient (r) and coefficient of variation (CV) were calculated. Linearity was established for the concentration/detector response relationship. The detection limit (LOD) was determined from the baseline noise at the peak retention time, defined as the mean noise plus three standard deviations. The limit of quantification (LOQ) was defined as ten times the standard deviation of the mean noise in blank determination.

Hormone analyses

The testosterone (YLA0007GO; sensitivity: 0.026 ng/ml), oestradiol (E2) (YLA0063GO; sensitivity: 0.57 ng/l), P4 (YLA0024GO; sensitivity: 0.024 ng/ml), FSH (YLA0061GO; sensitivity: 0.028 mIU/ml), and AMH (YLA0096GO; sensitivity: 2.39 pg/ml) levels in the goat blood sera were measured by an enzyme-linked immunosorbent assay (ELISA) using goat-specific commercial kits (YL Biont, Shanghai, P.R. China) according to the manufacturer's instructions. For all the hormone assays, the intra- and inter-assay CVs were <8% and <10%, respectively. An Infinite F50 microplate reader (Tecan, Grödig, Austria) was used to measure the absorbance of the colour that developed in the microplate at 450 nm. The hormone values are presented in the units specified in the commercially produced ELISA kits used in the analyses.

Statistical analysis

The data were analysed using the SPSS Statistics v21.0, developed by IBM Corporation. The normal distribution was evaluated using the Shapiro–Wilk test. Pearson correlation tests were applied to assess the relationship between the plasma meloxicam levels and the serum sex hormones, given the data's normal distribution. Independent samples T-tests and Mann–Whitney U tests were used to compare groups and examine differences in drug concentrations over time between male and female goats. The data are presented as the mean ± standard deviation (SD). $P < 0.05$ was used as the significance threshold in all the statistical analyses.

RESULTS

A correlation analysis was conducted to assess the relationships between the drug concentration and the testosterone, E2, P4, FSH, and AMH levels in male and female goats. The results indicated no significant relationship between the drug concentration and any of these hormones ($P > 0.05$). Figures 1–6 depict changes in drug concentrations and sex hormones, highlighting gender differences across time intervals. At time 0, the testosterone levels were significantly higher in males ($P < 0.001$), whereas the E2, P4 ($P < 0.05$),

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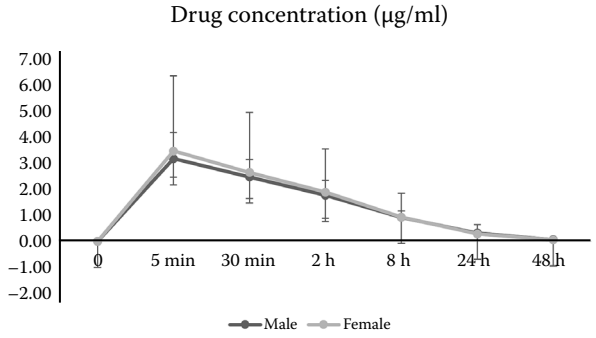

Figure 1. The difference in the plasma drug concentrations between male and female goats

Values are expressed as the mean value and standard deviation. No significant difference was observed between the male and female goats in plasma drug concentration ($P > 0.05$)

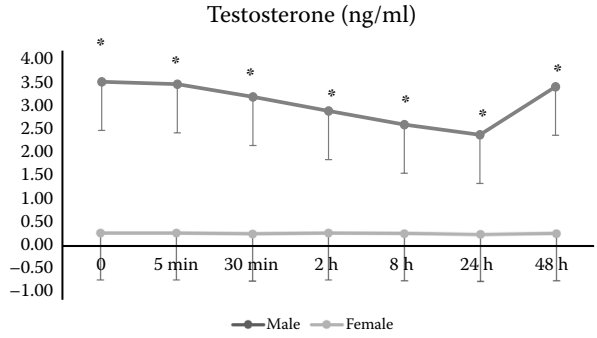

Figure 2. The difference in the serum testosterone concentrations between male and female goats

Values are expressed as the mean value and standard deviation. Asterisks (*) show the significant differences between the male and female goats serum testosterone levels ($P > 0.001$)

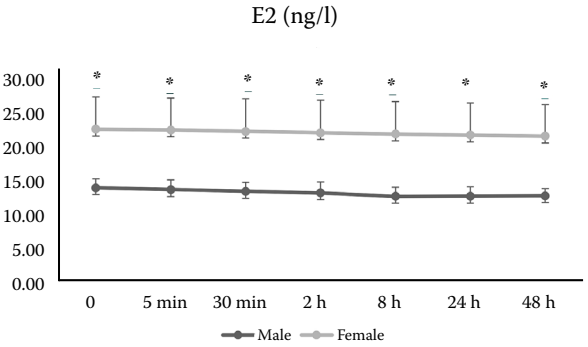

Figure 3. The difference in the serum oestradiol (E2) levels between male and female goats

Values are expressed as the mean value and standard deviation. Asterisks (*) show the differences between the male and female goats serum E2 levels ($P < 0.001$ and $P < 0.05$)

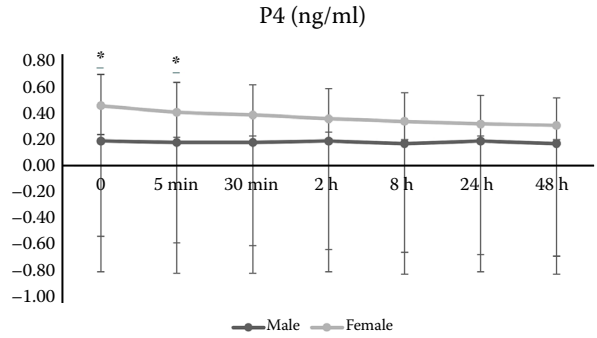

Figure 4. The difference in the serum progesterone (P4) concentrations between male and female goats

Values are expressed as the mean value and standard deviation. Asterisks (*) show the differences between the male and female goats serum P4 levels ($P < 0.05$)

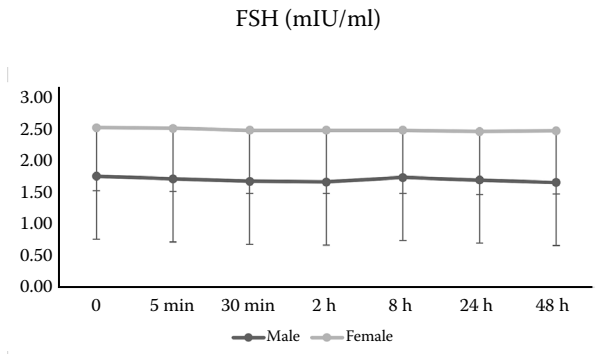

Figure 5. The difference in the serum follicle-stimulating hormone (FSH) concentrations between male and female goats

Values are expressed as the mean value and standard deviation. No significant difference was observed between the male and female goats in serum FSH levels ($P > 0.05$)

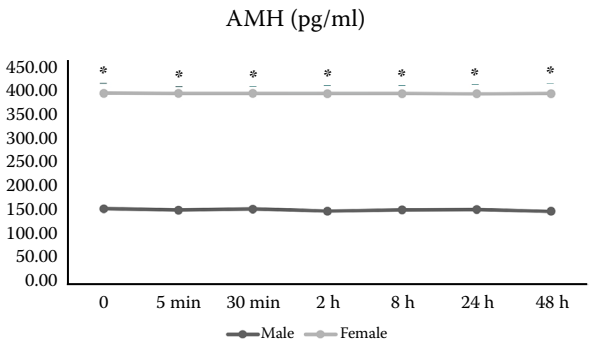

Figure 6. The difference in the serum anti-Müllerian hormone (AMH) concentrations between male and female goats

Values are expressed as the mean value and standard deviation. Asterisks (*) show the differences between the male and female goats serum AMH levels ($P < 0.001$)

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and AMH ($P < 0.001$) levels were significantly higher in females. No significant difference was observed in the FSH levels ($P > 0.05$). At all time points, the plasma drug concentration and FSH levels did not differ significantly between the male and female goats ($P > 0.05$). The testosterone levels remained significantly higher in males at all time points ($P < 0.001$). The progesterone levels were generally higher in females, with significant differences observed at time 0 and the 5 minutes ($P < 0.05$). Female goats had higher E2 and AMH levels than males at all time points. For E2, the differences were significant at $P < 0.05$ at time 0, 2 h, and 48 h, and at $P < 0.001$ at 5 min, 30 min, 8 h, and 24 hours. The AMH differences were consistently highly significant ($P < 0.001$) throughout the study, including at 48 hours.

DISCUSSION

In veterinary medicine, NSAIDs are frequently used to treat diseases (Clark-Price 2013). Meloxicam is a drug in the NSAID group and is widely used in the veterinary field (de la Puente et al. 2024). There are limited studies evaluating the relationship between the plasma drug concentrations of COX-2-selective NSAIDs, such as meloxicam, and gender-related differences in ruminants. The high COX-2 selectivity and lipophilic character of meloxicam raise the possibility of interaction with steroid hormones. In this study, the plasma meloxicam levels were evaluated at different time points. Although no significant difference in the plasma drug concentrations was found between the sexes, sex-related variations in hormone levels were evident. Testosterone levels were significantly higher in males, whereas E2 and AMH levels were consistently higher in females.

Studies have shown that steroid hormones such as testosterone and E2 affect the pharmacokinetics of drugs (Schwartz 2003; Mauvais-Jarvis et al. 2021). In humans, NSAIDs have been shown to inhibit androgen glucuronidation, primarily via UGT enzymes (Sten et al. 2009), and it is thought that similar mechanisms may apply in animal species. In this study, the meloxicam plasma concentrations did not differ between the sexes or correlate with the steroid hormone levels; however, it is important to consider that underlying hormonal variations may indirectly influence drug metabolism. In contrast to the present study, Corum et al. (2025) demonstrated that female Romanov sheep exhibited higher plasma meloxicam concentrations and longer elimination half-lives than males following intravenous administration, indicating that sex-based differences in the hepatic enzyme activity and physiological factors can significantly influence the drug disposition in ruminants. Importantly, the route of administration may further modulate these sex-related differences. In another pharmacokinetic study on Saanen goats, while sex differences in pharmacokinetics were limited following intravenous administration of meloxicam at 0.5 mg/kg, a pronounced divergence emerged after oral administration at 1 mg/kg, with male goats exhibiting significantly higher systemic exposure, longer mean residence times, and extended elimination half-lives compared to females. The calculated oral bioavailability was notably higher in males (104.73%) than in females (77.43%), suggesting that first-pass metabolism, differences in gastrointestinal absorption, and potential enterohepatic recirculation may amplify sex-related pharmacokinetic variability upon oral administration (Ozdemir Kutahya et al. 2025). These findings align with the evidence suggesting that sex-related physiological differences, including renal blood flow, body composition, and cytochrome (CYP) enzyme activity, can alter the drug disposition (Soldin and Mattison 2009; Spoletini et al. 2012). Notably, the faster clearance observed in male sheep was attributed to the higher CYP2C9 activity and increased renal elimination whereas the higher plasma concentrations in females may reflect reduced clearance and smaller distribution volumes.

To the best of our knowledge, no previous study has simultaneously evaluated time-dependent plasma meloxicam concentrations and sex hormone profiles in goats. Therefore, the interpretation of our findings relies largely on pharmacokinetic studies. While these studies (Corum et al. 2025; Ozdemir Kutahya et al. 2025) provide valuable biological context – demonstrating that sex can influence the hepatic enzyme activity, drug glucuronidation, and clearance rates – they do not directly address whether endogenous hormonal fluctuations modulate the short-term plasma concentrations of meloxicam. The lack of a direct correlation in our study suggests that meloxicam levels following intravenous administration may not be strongly influenced by short-term changes

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in hormone concentrations. It is also possible that any effects of sex hormones may manifest only through slower processes, such as changes in the liver enzyme activity over time, rather than through immediate interactions. This gap in the literature indicates that our study may help contribute basic information on how sex-related factors could influence NSAID use in small ruminants. Another consideration is that the intravenous administration bypasses the first-pass hepatic metabolism, which may reduce the likelihood of observing hormone-related variability in short-term plasma concentrations. Future studies involving oral administration, repeated dosing, or the direct assessment of the hepatic enzyme activity (UGT, CYP) may provide deeper insight into whether sex hormones exert delayed or pathway-specific effects on the meloxicam metabolism.

Furthermore, the amplification of sex differences with oral administration highlights the critical need to consider both the sex and administration route when evaluating drug pharmacokinetics and designing dosage regimens to optimise the therapeutic efficacy and ensure food safety in food-producing animals. In this study, only whether the blood levels of the lipophilic drug meloxicam after the intravenous administration were associated with plasma concentrations of sex hormones was investigated. Interestingly, no associations were found even with steroid hormones such as progesterone, testosterone, and oestradiol. Although no significant relationship was observed, the simultaneous analysis of both the hormone profiles and drug disposition in male and female goats provides valuable scientific insight.

This study investigated the impact of sex-related hormonal differences on the meloxicam concentrations at various sampling times in goats with seasonal polyoestrous cycles. Although no direct correlation was observed between meloxicam concentrations and the measured hormones – testosterone, oestradiol, progesterone, FSH, and AMH – clear sex-related differences in hormone profiles were evident throughout the sampling period. The absence of a significant association suggests that short-term plasma meloxicam concentrations are not directly modulated by circulating sex hormones under the conditions studied. However, the consistent hormonal differences observed indicate that sex-based physiological factors may still play a role in drug metabolism or disposition over longer periods or under different administration routes. Future research should explore these interactions using the hepatic enzyme activity, drug-protein binding rates, and extended sampling protocols to clarify the basis of sex differences in drug handling in goats. This research will be vital for guiding gender-specific drug use in goats.

Conflict of interest

The authors declare no conflict of interest.

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