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Comparative pharmacokinetic dispositions of omeprazole and its metabolites following intravenous and oral administration in sheep and goats

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ABSTRACT

This study aimed to determine the pharmacokinetic behavior of omeprazole (OMP) and its metabolites in sheep and goats following both intravenous (IV) and oral (PO) administration. Twelve one-year-old female animals, comprising six Awassi sheep and six Alpine goats, were used to compare pharmacokinetic parameters after a single dose of OMP (1.0 mg/kg IV and 4.0 mg/kg PO). Plasma levels of OMP, hydroxyomeprazole (OMP-OH), omeprazole sulfone (OMP-Sulfone), and omeprazole sulfide (OMP-Sulfide) were measured at specified time points. Results revealed that the pharmacokinetic profiles of OMP in sheep differed significantly from those in goats for both IV and PO routes. After IV administration, sheep showed greater systemic exposure (AUC0-∞: 1.84 ± 0.38 μg·h/mL) and a longer elimination half-life (T1/2λz: 0.26 ± 0.05 h) compared to goats (AUC0-∞: 0.67 ± 0.16 μg·h/mL; T1/2λz: 0.14 ± 0.03 h). Conversely, following PO administration, OMP bioavailability was low in both species, with sheep displaying an AUC0-∞ of 0.81 ± 0.38 μg·h/mL (F %: 11.00) and goats 0.33 ± 0.21 μg·h/mL (F %: 12.31). Metabolites OMP-OH and OMP-Sulfone were not detected in plasma after PO dosing in either species. However, after IV dosing, metabolite levels were higher in sheep than in goats. Consequently, these findings may support the development of more rational therapeutic strategies for the use of OMP in small ruminant medicine.

Introduction

Omeprazole (OMP), a proton pump inhibitor, is a benzimidazole derivative that is easily lipid-soluble and a weakly basic substance (Vanderhoff and Tahboub, 2002). Proton pump inhibitors (PPIs), including OMP, are used in humans to treat gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger-Ellison syndrome (ZES). They are also a key component of antibiotic therapy (amoxicillin and clarithromycin) for eradicating Helicobacter pylori in peptic ulcer disease (Welage and Berardi, 2000). The use of these agents is recommended for the prevention of stress-related and non-steroidal anti-inflammatory drug (NSAID)-induced peptic ulcer disease (Singh and Triadafilopoulos, 2005).

OMP undergoes extensive biotransformation in the body, resulting in the formation of multiple metabolites. The main metabolic pathway of OMP in humans involves CYP2C19, which converts it into hydroxyomeprazole (OMP-OH). Additionally, CYP3A4 metabolizes OMP to produce omeprazole sulfone (OMP-Sulfone) and omeprazole sulfide (OMP-Sulfide). Furthermore, OMP-Sulfone is metabolized by CYP2C19, yielding hydroxy omeprazole sulfone (Zhang et al., 2020). However, the two major metabolites, OMP-Sulfone and OMP-OH, do not contribute to antisecretory activity (Cederberg et al., 1989).

In ruminants, abomasal ulcer is a critical clinical condition that can affect animals of all ages, including lambs, calves, and kids, and is associated with economic losses due to reduced feed intake, milk yield, and growth performance (Vatn and Ulvund, 2000; Marshall, 2007; Constable et al., 2017). Its etiology includes nutritional disturbances, foreign body injury, increased abomasal acidity, prolonged NSAID use,

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fungal overgrowth, and stress-related factors (Fecteau and Whitlock, 2008).

OMP is sometimes used off-label to treat abomasal ulcers in ruminants. However, the unique anatomical and physiological features of the ruminant gastrointestinal system—including a complex, microbially active forestomach, variable ruminal pH, and prolonged gastrointestinal transit time may significantly affect the drug's oral absorption and systemic bioavailability, which differ from those in humans. Despite its clinical importance, there is no available information on the pharmacokinetics of OMP in small ruminants, especially after oral (PO) administration. Moreover, interspecies variations in metabolic enzyme activity can cause differences in systemic exposure and metabolite production. Therefore, understanding the pharmacokinetic profile of OMP in small ruminants is essential for developing evidence-based, safe, and effective dosing regimens.

We hypothesized that (1) the pharmacokinetic profile of OMP would vary between sheep and goats due to interspecies metabolic differences, and (2) oral administration of OMP in small ruminants would lead to low systemic bioavailability compared to intravenous (IV) administration. Based on these hypotheses, this study aimed to compare the pharmacokinetics and metabolite profiles of OMP following single-dose IV and oral administration in one-year-old ruminating Alpine goats and Awassi sheep, and to provide a scientific basis for the rational clinical use of OMP considering these interspecies differences.

Material and methods

Chemicals

Analytical standards for OMP (99.9%), OMP-Sulfone (H-168/66, 99.0%), OMP-OH (H-195/80, 89.0%) and OMP-Sulfide (H-168/22, 98.0%) were obtained from AstraZeneca, London, UK. The standards for lansoprazole (≥98.0%), HPLC grade acetonitrile (99.9%), sodium dihydrogen phosphate (99.0%), sodium chloride (99.8%), chloroform (99.8%), sodium hydroxide (99.0%), triethylamine (99.0%) and phosphoric acid (89%) were purchased from Sigma-Aldrich. Ultrapure water (18.2 MΩ.cm at 25°C) for preparing mobile phase, extraction, and analytical procedures was supplied by the Millipore Simplicity® water purification system (USA).

Animals

A total of 12 one-year-old ruminating female animals, including six Awassi sheep (30.98 ± 2.99 kg) and six Alpine goats (27.5 ± 1.46 kg), were used in this study. Before the experiment, all animals underwent thorough clinical examinations and hematological analyses to confirm their health status. None of the animals had received medication for at least two months prior to the study. The animals were divided into two groups based on species. They were fed commercial concentrate feed, while water and dry forage were provided ad libitum. The study protocol was approved by the Ethics Committee of Cukurova University, Health Sciences Experimental Application and Research Center.

Experimental design

The study employed a crossover design across two experimental periods, with a 10-day washout period between administration routes for sheep and goats. Commercially available injectable (Omeref, 40 mg/mL, Vem Pharmaceuticals) and powder (Gastroprazole, 2 g/sachet, Equi-tech) formulations of OMP were administered as a single dose of 1.0 mg/kg intravenously (Serih et al., 2024) and 4.0 mg/kg orally (Poulsen et al., 2005), respectively. OMP was initially administered IV during the first period and subsequently administered PO during the subsequent period. Both drug treatments were administered in the morning, before feeding the animals with a drug-free commercial concentrate. Throughout the study, the animals were monitored for any adverse reactions following administration of both IV and PO OMP. Blood samples (3 mL) were collected into heparinized tubes before drug administration (time 0) and subsequently at 5, 10, 20, 30, and 45 min, and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h post-administration. The samples were centrifuged within one hour of collection, and plasma was stored at −80 °C until further analysis. Although OMP is acid-labile, previous reports indicate acceptable stability under frozen conditions; however, stability was not specifically evaluated in sheep and goat plasma.

Analytical procedure

Instrumentation

Chromatographic analyses were conducted using an Agilent 1260 HPLC system (Agilent, Germany) featuring a binary high-pressure isocratic configuration. An Agilent binary pump (G1312B) was employed to deliver the mobile phase to the analytical column. Sample injection was carried out via an Agilent autosampler (G1367E) coupled with an injection valve (Rheodyne®, USA) equipped with a 100-µL variable loop. Detection was performed using a photodiode array (PDA) detector (G4212B) in accordance with the data acquisition software, ChemStation, from Agilent (Germany). Degassing of the mobile phase was accomplished using an Agilent vacuum degasser unit (G4225A). The operation and functions of the entire HPLC system were managed by ChemStation® Software (C.01.08, Agilent, Germany).

Chromatographic conditions

An analytical column (Luna C18, 5 µm, 250 mm×4.6 mm, Phenomenex) with a nucleosil C18 guard column (Phenomenex, UK), kept at 50 °C during analysis in a column oven (G1316A), was used to separate OMP and its metabolites. The mobile phase, consisting of acetonitrile and ultra-pure water (H2O) (30:70, pH 3.5 with phosphoric acid), was delivered in an isocratic mode at a flow rate of 1 mL/min. The photodiode array (PDA) detector (G4212B) was set at 292 nm. The injection volume was 30 µL throughout the study, and chromatographic analysis of plasma samples was completed within 14 min after injection.

Preparation of analytical standard solutions

Stock analytical standard solutions (500 µg/mL) of OMP and its metabolites (OMP-OH, OMP-Sulfide, and OMP-Sulfone), along with the internal standard lansoprazole (5 µg/mL), were prepared in methanol: ultra-pure water (50:50) and stored in glass bottles at 4°c. These solutions were then diluted with methanol:ultra-pure water to produce concentrations of 0.1, 0.5, 5, and 25 µg/mL for plasma sample analysis. They were used to spike drug-free plasma at various concentrations to generate standard curves and assess the recovery of the extraction process.

Sample preparations and extraction procedures

The plasma concentrations of OMP and metabolites were measured using HPLC after liquid-liquid phase extraction, following the method described by Serih et al. (2024) with minor modifications as outlined below. Blank plasma samples (0.25 mL) were spiked with OMP standard solutions to achieve final concentrations of 0, 0.05, 0.1, 0.5, 1, 5, and 10 µg/mL for the IV study, and 0, 0.05, 0.1, 0.5, 1, and 5 µg/mL for the PO study. Both spiked and experimental plasma samples were combined with 50 µL of internal standard (lansoprazole 5 µg/mL). Next, sodium chloride (0.05 g) was added and vortexed for 1 min, followed by the addition of 2 mL of chloroform, which was vortexed for another minute. The mixture was then centrifuged at 12,000 rpm for 5 min. The supernatant was discarded, and the lower organic phase was transferred to a 10 mL glass tube and evaporated in a vacuum concentrator (Maxi-dry® plus, Heto Lab. Equipment, Denmark) at 30 °c. The thoroughly dried residue was dissolved in 200 µL of methanol:ultra-pure water (30:70, pH 10 with triethylamine) and vortexed briefly for 15 s. Finally, 30 µL of this solution was injected into the HPLC system for analysis.

Validation of the analytical method

The analytical methods employed to determine OMP and its metabolites in sheep and goat plasma samples were validated prior to the analysis of the experimental samples. This validation adhered to the International Conference on Harmonization (ICH) guidelines for the validation of analytical procedures (International Council for Harmonization ICH, 2005).

The analytes were identified by their retention times matching those of the reference standards. Recoveries of the target molecules were determined by comparing the peak areas of spiked sheep and goat plasma samples with those obtained from direct injections of standards prepared in methanol:ultra-pure water. The precision within and between assays was assessed by analysing replicate aliquots of drug-free goat and sheep plasma samples spiked with known drug amounts on different days. Calibration graphs for OMP and its metabolites were constructed, with a linear range of 0.05–10 μg/mL for the IV study and 0.05–5 μg/mL for the oral study. The slope of the calibration lines was derived using least squares linear regression, and the correlation coefficient (r) and coefficient of variation (CV) were calculated. Linearity was established to evaluate the relationship between OMP and metabolites concentrations and detector response. Detection limits for OMP and its metabolites were determined using HPLC analysis of blank plasma samples fortified with standards, by measuring baseline noise at the retention times of the peaks. The detection limit (LOD) was defined as the mean baseline noise plus three standard deviations (SDs). The limit of quantification (LOQ) was set at the mean baseline noise plus nine SDs.

The plasma concentrations *vs.* time curves obtained after each treatment in individual animals were fitted with the WinNonlin software program (Version 5.2, Pharsight Corporation, Mountain View, CA, USA). The pharmacokinetic parameters for each animal were analysed using non-compartmental model analysis. The maximum plasma concentration (C_{max}) and time to reach maximum concentration (T_{max}) were obtained from the plotted concentration-time curve of the drug in each animal. The trapezoidal rule was used to calculate the area under the plasma concentration-time curve (AUC).

The mean residence time (MRT) was calculated as:

$$MRT_{0\rightarrow\infty} = AUMC_{0\rightarrow\infty} / AUC_{0\rightarrow\infty}$$

Terminal half-life ($T_{1/2\lambda z}$) was calculated as:

$$T_{1/2\lambda z} = -\ln(2)/\lambda z$$

Where λz represents the first-order rate constant associated with the terminal (log-linear) portion of the curve.

The fraction of dose absorbed (ie, *F* %) was calculated by use of mean AUCs calculated for each route of administration by use of the following equation, following dose normalization:

$$F\ (\%) = (AUC_{PO} \times DOSE_{IV}) / (AUC_{IV} \times DOSE_{PO}) \times 100$$

Statistical analysis

Pharmacokinetic parameters are presented as mean ± SD. Harmonic means were calculated for T1/2λz, MRTlast, and MRT0-∞ . For the comparison of administration routes, non-normally distributed data were analysed using the non-parametric Wilcoxon signed-rank test, whereas normally distributed data were assessed using the paired *t*-test. When comparing species, non-normally distributed data were tested with the non-parametric Mann-Whitney *U* test, and normally distributed data were analysed using the independent *t*-test. All statistical analyses were performed with SPSS Statistics version 23.0 (IBM Corp).

Results

The validation parameters of OMP and its metabolites for the analysis of sheep and goat plasma samples are given in Table 1. The sulfide metabolite (OMP-Sulfide) of OMP was not detected above the LOQ value in any plasma sample from either sheep or goats following IV and PO administration. Moreover, following intravenous administration, at least two unidentified peaks belonging to potential metabolites were observed in both sheep and goat IV samples. The peak heights of these unidentified metabolites were higher than those of the known metabolites. In addition, OMP-OH and OMP-Sulfone metabolites were not detected above the LOD value in the plasma samples following PO administration in both species.

No adverse effects were observed in the sheep and goats used for this study. None of the animals showed altered appetite or signs of anaphylaxis. In this study, the pharmacokinetic profile of OMP and the plasma levels of its metabolites, OMP-OH and OMP-Sulfone, were comparatively evaluated in Awassi sheep and Alpine goats following IV administration. The results (Table 2) indicated that following IV administration, OMP was rapidly eliminated in both species; however, systemic exposure and initial plasma concentrations were significantly higher in sheep. The elimination half-life ($T_{1/2\lambda z}$) and mean residence time ($MRT_{0-\infty}$) of OMP were also significantly longer in sheep compared to goats. Similarly, the OMP-OH metabolite (Table 3) exhibited a delayed time to peak concentration, greater systemic exposure, and longer residence time in sheep. A comparable trend was observed for OMP-Sulfone (Table 4), with higher $T_{1/2\lambda z}$ and increased $AUC_{0-\infty}$ in sheep. In goats, the pharmacokinetic parameters of both the main compound and the metabolites were characterized by faster elimination, lower AUC and shorter MRT values. Following IV administration, OMP and OMP-OH were detectable in plasma for up to 2 h in sheep and one h in goats (Fig. 1 and Fig. 2, respectively), whereas OMP-Sulfone was quantifiable for up to 1 h in sheep and 0.75 h in goats (Fig. 3).

After PO administration of OMP to sheep and goats, the metabolites (OMP-Sulfide, OMP-OH and OMP-Sulfone) were not detectable in plasma. The pharmacokinetic parameters of orally administered OMP (4.0 mg/kg) in both species are presented in Table 5, along with the plasma concentration-time curves (Fig. 4). Oral OMP showed low systemic exposure in both species, with sheep exhibiting higher plasma concentrations and greater AUC values than goats. The T_{max} was earlier in sheep, whereas goats displayed a delayed absorption profile. However, the reliability of pharmacokinetic parameters, including the elimination half-life of OMP after PO dosing, should be considered, given that concentrations were near the LOQ and may be subject to error.

Discussion

The pharmacokinetic parameters of OMP and the plasma levels of its metabolites were determined following a single IV administration at a dose of 1.0 mg/kg and a single PO administration at 4.0 mg/kg in one-year-old ruminating sheep and goats using a crossover design in this study. The results demonstrated that IV administration resulted in a shorter $T_{1/2\lambda z}$ and a greater AUC compared to PO administration in both species.

The pharmacokinetic assessment of OMP in sheep and goats revealed species-specific differences in disposition. In both species, OMP was rapidly eliminated from plasma, but sheep exhibited higher systemic exposure and slower clearance than goats. The shorter half-life in goats, along with their larger volume of distribution (Vd) and faster clearance, indicates a more extensive tissue distribution and quicker drug elimination compared to sheep. These parameters highlight fundamental metabolic and physiological differences that influence OMP disposition in small ruminants. The previous studies indicated that goats metabolize and eliminate compounds more rapidly than sheep (Bogan et al., 1987; Gokbulut et al., 2014; Aksit et al., 2015; Fadel et al., 2025), which is consistent with the findings of the present study. The pharmacokinetic profile of OMP in one-year-old ruminating sheep and goats following IV administration was compared with the findings reported by Serih et al.

Table 1
Validation parameters of the analytical method used for the determination of omeprazole (OMP) and its metabolites in sheep and goat plasma samples, respectively.

	Molecules	LOD (µg/mL)	LOQ (µg/mL)	Range of linearity (µg/mL)	Linearity (r^2)	Recovery (%)	Coefficient of variation (%)
Sheep	**OMP**	0.012	0.04	0.05–10	0.998	95.58 (4.99)*	5.22
	OMP-Sulfone	0.010	0.032	0.05–10	0.999	100.11 (4.19)*	4.82
	OMP-OH	0.016	0.05	0.05–10	0.997	100.86 (4.24)*	4.55
	OMP-Sulfide	0.008	0.025	0.05–10	0.999	85.79 (3.42)*	3.57
Goat	**OMP**	0.012	0.04	0.05–10	0.999	94.12 (4.43)*	4.71
	OMP-Sulfone	0.011	0.035	0.05–10	0.999	94.29 (6.30)*	6.69
	OMP-OH	0.017	0.05	0.05–10	0.997	80.60 (4.7)*	5.79
	OMP-Sulfide	0.009	0.030	0.05–10	0.998	84.50 (4.52)*	6.16

LOD: Limit of detection, LOQ: Limit of quantification, *r*: correlation coefficient.
* Values in the brackets represent the standard deviations for the recovery assays (n = 6).

Table 2
Pharmacokinetic parameters of omeprazole (1.0 mg/kg) after intravenous (IV) administration to sheep and goats (n = 6).

Parameters	Sheep	Goat
$T_{1/2\lambda z}$ (h)[a]	0.26 ± 0.05	0.14 ± 0.03*
C_0 (µg/mL)	5.75 ± 0.76	3.90 ± 0.47*
AUC_{last} (µg.h/mL)	1.81 ± 0.37	0.67 ± 0.15*
$AUC_{0-\infty}$ (µg.h/mL)	1.84 ± 0.38	0.67 ± 0.16*
$AUMC_{last}$ (µg.h^2/mL)	0.61 ± 0.18	0.11 ± 0.05*
$AUMC_{0-\infty}$ (µg.h^2/mL)	0.66 ± 0.20	0.12 ± 0.06*
MRT_{last} (h)[a]	0.32 ± 0.05	0.16 ± 0.03*
$MRT_{0-\infty}$ (h)[a]	0.35 ± 0.05	0.17 ± 0.04*
Vd_{ss} (L/kg)	0.20 ± 0.03	0.26 ± 0.04*
Cl (L/h/kg)	0.59 ± 0.13	1.55 ± 0.33*

$T_{1/2\lambda z}$: terminal half-life; C_0: calculated concentration at time zero of IV administration, AUC: area under the (zero moment) curve from time 0 to the last detectable concentration, AUMC: area under the moment curve from time 0 to t last detectable concentration, MRT: mean residence time; Vd_{ss}, volume of distribution at steady-state; Cl, clearance of drug.
[a]Harmonic mean.
*The kinetic parameters in goats are significantly different ($P < 0.05$) from those in sheep.

Table 3
Pharmacokinetic parameters of hydroxyomeprazole (OMP-OH) after intravenous (IV) administration of omeprazole (1.0 mg/kg) to sheep and goats (n = 6).

Parameters	Sheep	Goat
$T_{1/2\lambda z}$ (h)[a]	0.53 ± 0.06	0.32 ± 0.09*
T_{max} (h)	0.28 ± 0.09	0.14 ± 0.04*
C_{max} (µg/mL)	0.64 ± 0.10	0.60 ± 0.15
AUC_{last} (µg.h/mL)	0.59 ± 0.08	0.28 ± 0.07*
$AUC_{0-\infty}$ (µg.h/mL)	0.66 ± 0.12	0.36 ± 0.06*
$AUMC_{last}$ (µg.h^2/mL)	0.39 ± 0.08	0.09 ± 0.03*
$AUMC_{0-\infty}$ (µg.h^2/mL)	0.58 ± 0.17	0.20 ± 0.07*
MRT_{last} (h)[a]	0.65 ± 0.07	0.33 ± 0.05*
$MRT_{0-\infty}$ (h)[a]	0.84 ± 0.10	0.52 ± 0.14*

$T_{1/2\lambda z}$: terminal half-life, T_{max}: time to reach peak plasma concentration, C_{max}: peak plasma concentration, AUC: area under the (zero moment) curve from time 0 to the last detectable concentration, AUMC: area under the moment curve from time 0 to t last detectable concentration, MRT: mean residence time.
[a]Harmonic mean.
*The kinetic parameters in goats are significantly different ($P < 0.05$) from those in sheep.

(2024). The researchers identified similar findings to our study, and this difference may be related to individual metabolic rate, liver enzyme activity, or post-administration distribution patterns. The Vd reported

Table 4
Pharmacokinetic parameters of omeprazole sulfone (OMP-Sulfone) after intravenous (IV) administration of omeprazole (1.0 mg/kg) to sheep and goats (n = 6).

Parameters	Sheep	Goat
$T_{1/2\lambda z}$ (h)[a]	0.35 ± 0.06	0.16 ± 0.08*
T_{max} (h)	0.18 ± 0.08	0.10 ± 0.03*
C_{max} (µg/mL)	0.10 ± 0.01	0.10 ± 0.10
AUC_{last} (µg.h/mL)	0.06 ± 0.01	0.03 ± 0.05
$AUC_{0-\infty}$ (µg.h/mL)	0.07 ± 0.02	0.04 ± 0.06
$AUMC_{last}$ (µg.h^2/mL)	0.02 ± 0.01	0.01 ± 0.02
$AUMC_{0-\infty}$ (µg.h^2/mL)	0.05 ± 0.02	0.02 ± 0.03
MRT_{last} (h)[a]	0.40 ± 0.04	0.16 ± 0.09*
$MRT_{0-\infty}$ (h)[a]	0.60 ± 0.10	0.29 ± 0.13*

$T_{1/2\lambda z}$: terminal half-life, T_{max}: time to reach peak plasma concentration, C_{max}: peak plasma concentration, AUC: area under the (zero moment) curve from time 0 to the last detectable concentration, AUMC: area under the moment curve from time 0 to t last detectable concentration, MRT: mean residence time.
[a]Harmonic mean.
*The kinetic parameters in goats are significantly different *(P < 0.05)* from those in sheep.

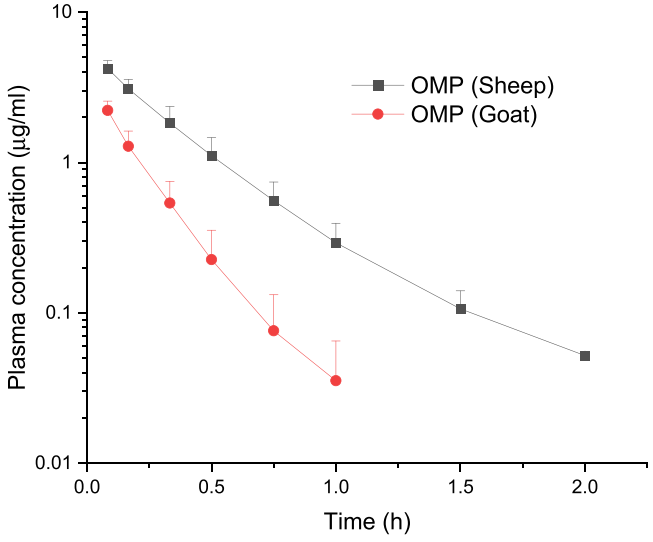

Fig. 1. Comparative mean (±SD) plasma concentration *vs.* time curves of OMP in sheep and goats following intravenous administrations at a dose of 1.0 mg/kg (n = 6).

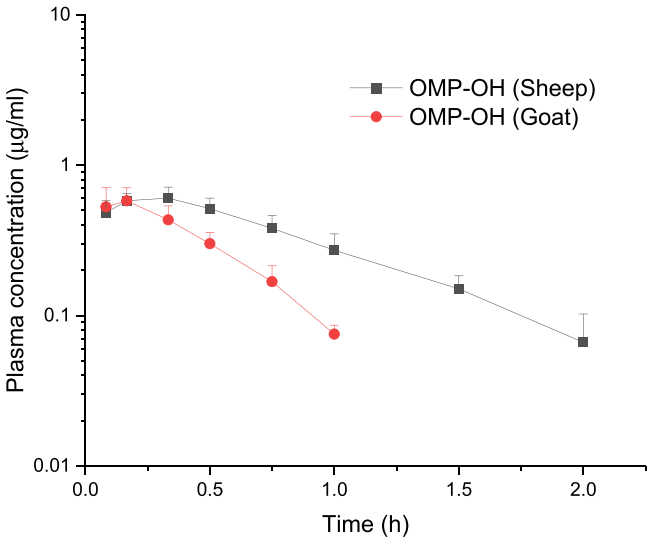

Fig. 2. Comparative mean (±SD) plasma concentration *vs.* time curves of OMP-OH in sheep and goats following intravenous administrations of OMP at a dose of 1.0 mg/kg (n = 6).

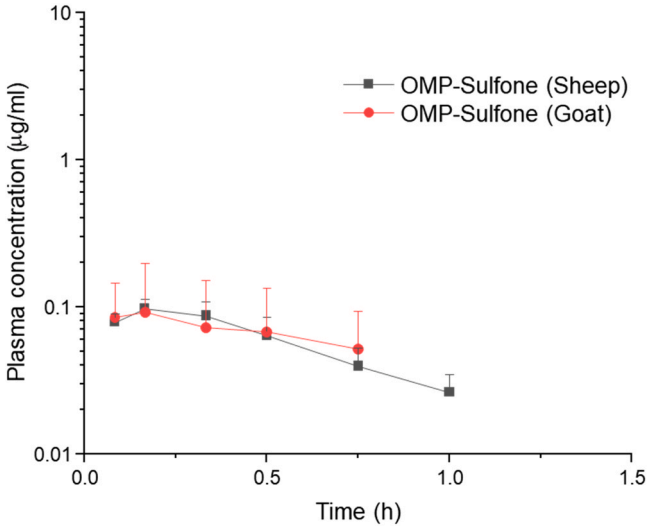

Fig. 3. Comparative mean (±SD) plasma concentration *vs.* time curves of OMP-Sulfone in sheep and goats following intravenous administrations of OMP at a dose of 1.0 mg/kg (n = 6).

by Serih et al. (2024) in goats was markedly higher than in the present study. This difference may be related to pharmacokinetic variables such as plasma protein binding level, tissue penetration mechanisms or individual metabolic differences.

In our study, the systemic exposure of OMP was lower than that previously reported for pantoprazole and esomeprazole. Similar to our findings, OMP was cleared more rapidly than previously reported for both pantoprazole and esomeprazole (Smith et al., 2021; Fladung et al., 2022; Smith et al., 2023; Fadel et al., 2024). Although we observed no significant interspecies differences in the Vd, OMP generally showed a more limited tissue distribution compared with the other PPIs (Smith et al., 2021; Fladung et al., 2022; Smith et al., 2023; Fadel et al., 2024).

This study is the first to evaluate the pharmacokinetics of OMP administered orally to sheep and goats. After oral administration, OMP showed low bioavailability in sheep (F%: 11.00) and goats (F%: 12.31). These results support the idea that oral absorption of OMP in ruminants is limited, mainly due to drug degradation in the forestomach

Table 5
Pharmacokinetic parameters of omeprazole (4.0 mg/kg) after oral (PO) administration to sheep and goats (n = 6).

Parameters	Sheep	Goat
$T_{1/2\lambda z}$ (h)[a]	1.35 ± 0.92	0.85 ± 0.71
T_{max} (h)	1.29 ± 0.90	2.08 ± 0.97
C_{max} (µg/mL)	0.31 ± 0.17	0.09 ± 0.04
AUC_{last} (µg.h/mL)	0.73 ± 0.35	0.30 ± 0.18*
$AUC_{0-\infty}$ (µg.h/mL)	0.81 ± 0.38	0.33 ± 0.21*
$AUMC_{last}$ (µg.h^2/mL)	1.64 ± 0.81	0.89 ± 0.73
$AUMC_{0-\infty}$ (µg.h^2/mL)	2.53 ± 1.57	1.22 ± 1.02
MRT_{last} (h)[a]	2.08 ± 0.58	2.15 ± 1.01
$MRT_{0-\infty}$ (h)[a]	2.60 ± 1.10	2.58 ± 1.27
F (%)	11.00	12.31

$T_{1/2\lambda z}$: terminal half-life, T_{max}: time to reach peak plasma concentration, C_{max}: peak plasma concentration, AUC: area under the (zero moment) curve from time 0 to the last detectable concentration, AUMC: area under the moment curve from time 0 to t last detectable concentration, MRT: mean residence time, *F*: bioavailability.
[a]Harmonic mean.
*The kinetic parameters in goats are significantly different ($P < 0.05$) from those in sheep.

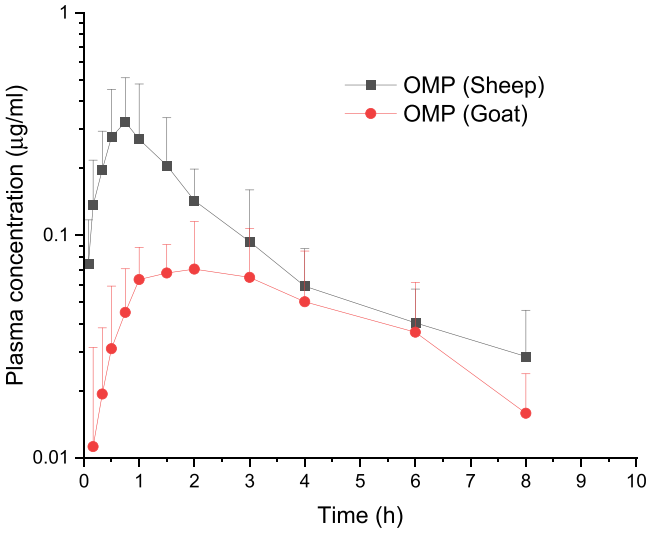

Fig. 4. Comparative mean (±SD) plasma concentration *vs.* time curves of OMP in sheep and goats following *per os* administrations at a dose of 4.0 mg/kg (n = 6).

environment and the effects of first-pass metabolism. (Christensen et al., 2001; Poulsen et al., 2005). Furthermore, the prolonged T_{max} values observed after PO administration indicate that the drug's gastrointestinal absorption is slow and inconsistent. The complex anatomy and physiology of the fore-stomachs, including large volume, stratified contents, slow transit time, and microbial activity, likely contribute to the slower and inconsistent absorption observed after PO administration. These results suggest that the clinical efficacy of PO OMP formulations in ruminants may be limited.

There is no available information on the disposition of OMP and its metabolites in small ruminants. Although the metabolites of OMP, OMP-OH and OMP-Sulfone, are not pharmacologically active (Cederberg et al., 1989), this study is the first to report plasma concentrations of OMP metabolites (OMP-OH and OMP-Sulfone) following IV administration in sheep and goats. Metabolite analysis showed significant interspecies differences in the plasma levels of OMP-OH and OMP-Sulfone after IV administration of OMP. Both the half-lives and AUCs of these metabolites were higher in sheep than in goats, indicating species-specific variation in the rate of metabolic transformation. Previous research has indicated that OMP metabolism varies across species,

particularly in hepatic enzyme activity, which affects the drug's pharmacokinetics (Hoffmann, 1986; Andersson et al., 1991). Plasma levels of OMP metabolites after PO administration were below the LOD of the assays, demonstrating limited bioavailability of the drug. This may be due to the rapid degradation of OMP in the highly acidic environment of the ruminants' foregut. Additionally, since OMP metabolites lack antisecretory activity (Cederberg et al., 1989) and were detected at low levels in sheep and goats, these findings suggest species-specific metabolic differences; however, the clinical significance of this observation requires further pharmacodynamic study. These results underscore the importance of exploring different formulations and dosage regimens in future research.

In HPLC analyses, we observed at least two unidentified peaks that may represent metabolites in both sheep and goat IV samples. These peaks were higher than those of known metabolites. This indicates that the metabolic pathways of OMP in sheep and goats may differ considerably from those in humans. Unfortunately, we were unable to identify these peaks due to the absence of an LC-MS/MS system, which was a limitation of this study. Consequently, further research is needed to understand interspecies differences in OMP metabolism.

In conclusion, the current findings demonstrate that the pharmacokinetic profile of OMP varies between sheep and goats, reflecting interspecies metabolic differences, and PO administration of OMP results in low systemic bioavailability compared to IV dosing. This variation may be due to differences in metabolic pathways involving the hepatic enzyme systems of sheep and goats, as well as the drug-metabolizing ruminal microflora. Given the low oral bioavailability, intravenous or subcutaneous formulations remain more appropriate for clinical use in small ruminants until improved enteric delivery systems become available. Although pharmacodynamic data are currently lacking, understanding the pharmacokinetics of OMP can help inform more rational dosing strategies and reduce the risk of adverse effects. Future studies investigating metabolic pathways and pharmacodynamics, and establishing suitable dosage regimens, will further support the safe and effective use of OMP in these species.

Animal welfare and ethics statement

All protocols in animals were approved (approval code: 1, approval date: 27.06.2024) by the Ethics Committee of the Cukurova University, Health Sciences Experimental Application and Research Center and carried out in accordance with the European Directive (2020/63/UE).

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CRediT authorship contribution statement

Zeynep Ozdemir Kutahya: Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Conceptualization. **Selen Mamuk:** Methodology. **Busra Aslan Akyol:** Writing – original draft, Methodology. **Cengiz Gokbulut:** Writing – review & editing, Software, Project administration, Methodology.

Declaration of Generative AI and AI-assisted technologies in the writing process

Grammarly was used for proofreading the English. The authors have reviewed and edited the results and take full responsibility for the content of this publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The data supporting the study's results are available from the corresponding author on reasonable request.

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