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Pharmacokinetics of famotidine in goats after intravenous administration

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Abstract

There is currently limited pharmacokinetic data for the use of famotidine in goats for treatment and prevention of abomasal ulceration. The objective of this study was to determine the pharmacokinetic parameters after a single intravenous administration of famotidine (0.6mg/kg). Famotidine was administered to six healthy goats and plasma samples were collected over a 24-hour period. The famotidine concentration was measured using reverse phase high performance liquid chromatography (HPLC). Non-compartmental analysis was then used to determine the pharmacokinetic parameters. The maximum plasma concentration was estimated at 5476.68 ± 1530.51 ng/mL and elimination half-life was estimated at 18.455 ± 13.26 min. The mean residence time was determined to be 19.85 ± 12.14 min with the apparent volume of distribution being estimated at 321.924 ± 221.667 . The area under the curve was determined to be 54230.08 ± 24947.6 min*ng/mL. Total exposure and elimination half-life were less than what has been reported in cattle and horses. Future research evaluating the pharmacokinetics of subcutaneous administration as well as looking at the pharmacodynamics of famotidine in goats is needed to determine the effectiveness of famotidine on raising pH levels of the abomasum.

Keywords: Abomasal ulceration, ruminant, gastric, gastroprotectant, histamine

1 Introduction

Famotidine (C₈H₁₅N₇O₂S₃) is a histamine type-2 (H₂) receptor antagonist drug which blocks H₂ receptors and as a result decreases acid secretion. (Marks, Kook, Papich, Tolbert, & Willard, 2018) Another type of drug used to decrease acid secretion is proton pump inhibitors such as omeprazole. The benefits of using famotidine instead of omeprazole is that famotidine is less expensive, is maximally effective within hours of administration, and has been shown to have additional healing effects including increased mucus and bicarbonate secretion. (Tolbert et al., 2017) Additionally, chronic use of proton pump inhibitor drugs has been linked to adverse effects in humans such as decreased bone mineral content, increased risk for developing community-acquired pneumonia, and *Clostridium difficile*-associated diarrhea. (Tolbert et al., 2017) Compared to other H₂ antagonist drugs, famotidine has been found to be more effective than those such as ranitidine and cimetidine in studies investigating its use in dogs. (Duran, 2003)

Famotidine is often used in small animal medicine to treat dogs and cats for stomach ulceration, acid reflux, and inflammation of the stomach and esophagus.

In human studies, famotidine has been found to be effective at treating and preventing gastric and duodenal ulceration (Taha et al., 1996), affecting only the gastric parietal cells with no effect on H-2 receptors outside the gastrointestinal tract. (Al-Omar & Al-Mohizea, 2009) Famotidine has been shown to have the least amount of side effects in addition to high tolerability compared to other drugs of the class. (Al-Omar & Al-Mohizea, 2009) After intravenous administration in humans, the elimination half-life was found to be 2 to 4 hours and the steady state volume of distribution was found to be 1.0 to 1.3 l/kg. (Echizen & Ishizaki, 1991)

Small ruminants, such as goats, are susceptible to abomasal ulceration caused by stress, disease, or reaction to medications. (Hund & Wittek, 2018; Smith, Kosusnik, & Mochel, 2020) There are levels to which ulceration occurs ranging from type 1 (nonperforating) to type 4 (perforating) with the spread of ingesta throughout the peritoneal cavity. (Hund & Wittek, 2018) Several studies reporting abomasal ulceration in cattle have shown fatality in those with perforating ulcers. (Hund & Wittek, 2018) There have been several suggested treatments for ulceration in other species including the histamine type-2 receptor antagonist drugs. (Marks et al., 2018) Despite evaluations of famotidine in cattle being reported, there is currently a paucity of information in small ruminants regarding famotidine for treatment or prevention of gastric ulceration in goats. The goal of this study was to report the pharmacokinetics of a single intravenous administration of famotidine in goats.

2 Material and Methods

2.1 Animals

Six healthy goats were used during this study. During the study they were fed a diet of *ad libitum* grass hay. Before the study was conducted the goats were all deemed healthy based on physical examination by a large animal veterinary specialist. They were housed at the University of Tennessee College of Veterinary Medicine. This study was approved by the University of Tennessee Institutional Animal Care and Use Committee (Protocol #2979-0423).

2.2 Sample Collection

Famotidine dosed at 0.6 mg/kg was administered intravenously through a catheter in the right jugular vein of the neck. Blood samples were collected through another intravenous catheter on the left jugular vein. Samples were collected at: 0 (before famotidine administration), 2, 10, 30, and 45 minutes and 1, 2, 4, 6, 8, 12, and 24 hours after administration. For sample collection the catheter was flushed with 0.9% saline and the push-pull technique (Hess & Decker, 2017) was used to ensure the catheter was clear of any blood from a previous pull. Once collected the blood was placed in a heparinized tube and immediately placed on ice. The blood was then centrifuged at 1500 x g for 10 minutes. After being spun down, the plasma was pipetted into criovials and stored at -80°C for analysis.

2.3 Analytical Chemistry

Analysis of famotidine in plasma samples was conducted using reversed phase HPLC. The system consisted of a 2695 separations module and a 2487 ultraviolet detector (Waters, Milford, MA, USA.). Separation was attained on a Waters XBridge C₈ 4.6 x 250mm (5 μm) with a XBridge guard column. The mobile phase consisted of 20 mM sodium acetate (pH 5.5) and acetonitrile (91:9). The drug was quantified using UV detection at 267 nm for famotidine and 230 nm for cimetidine and the flow rate was 0.9 ml/min. The column was at ambient temperature.

Samples that were previously frozen were thawed at room temperature, mixed, and 250 μl of plasma was transferred to a 16 x 100 mm tube followed by 50 μl of cimetidine (internal standard, 1 μg/mL), and 1 mL of 0.1 M sodium hydroxide. Samples were vortexed for 30 seconds and underwent centrifugation for 10 minutes. The mixture was passed through a prewet Oasis HLB 1cc (30mg) solid phase extraction cartridge (Waters). The column was washed with 1 mL of 5% methanol. Samples were eluted with 2 mL of methanol then evaporated with nitrogen. Residues were reconstituted in 250 μL of mobile phase and 100 μL injected into the HPLC.

Standard curves for the plasma analysis were prepared by fortifying untreated, pooled plasma with famotidine, which produced a linear concentration range of 5-5000 ng/mL. The recovery for famotidine averaged 93% while the internal standard average was 98%. The assay variability was less than 10% and the lower limit of quantification was 5 ng/mL.

2.4 Pharmacokinetic Analysis

A non-compartmental approach was used for evaluation of famotidine in plasma after intravenous administration for each goat using commercially available pharmacokinetic software (PKanalix, Monolix Suite 2021R1, Lixoft, France). Maximum concentration (C_{max}) was taken directly from data observation. Analysis used raw data and was expressed using the statistical moments theory and standard formulas for intravascular injection including:

1. Area under the famotidine concentration-time curve to the last measurable plasma concentration AUC_{last} .
2. Area under the moment curve, $AUMC_{last}$.
3. Famotidine mean residence time, $MRT = AUMC_{last}/AUC_{last}$.
4. Famotidine elimination rate, λ_z .
5. Famotidine terminal half-life, $T_{1/2}(\lambda_z) = \ln(2)/\lambda_z$.
6. Famotidine systemic clearance, $CL = Dose/AUC_{last}$
7. Volume of distribution, V_z .
8. Volume of distribution of famotidine at a steady state, $V_{ss} = CL \times MRT$

The linear/trapezoidal linear/log rule was used for the data analysis in order to estimate area under the famotidine time curves. A summary of the statistics was performed thereafter to derive the geometric mean and range of the individual pharmacokinetic parameters. The famotidine intravenous administration is reported as described above in addition to reporting for the individual goats.

3 Results

3.1 Animals

The goats were monitored and a physical exam including obtaining a temperature, heart rate, respiratory rate, and rumen contraction rate was performed daily. There were no adverse effects observed in any of the goats used in the study.

3.2 Pharmacokinetics

The time vs concentration for famotidine after intravenous administration (n=6) is shown in **Figure 1**. The pharmacokinetic parameters for famotidine after intravenous administration are shown in **Table 1**. The individual pharmacokinetic parameters for all six goats are presented in **Table 2**. The plasma was analyzed for presence of famotidine for all time points except for any after there had been no famotidine detected for two time points continuously. There was no famotidine detected after four hours post administration. The initial concentration (C_0) was 5476.68 ± 1530.51 ng/mL.

4 Discussion

The pharmacokinetic of famotidine (0.6mg/kg) after single intravenous administration in goats was investigated in this study. To the author's knowledge, while the pharmacokinetics of famotidine are described for cattle (Balcomb, Heller, Chigerwe, Knych, & Meyer, 2018), there are currently no prospective studies in goats determining the pharmacokinetics of famotidine.

Abomasal ulceration is thought to be connected to histamine expression. (Hund & Wittek, 2018) Famotidine, which targets and blocks the histamine-2 receptor would, therefore, be beneficial for ulceration treatment. There are other histamine-2 receptor antagonists such as ranitidine and cimetidine, however, famotidine has been found to be more potent at suppressing histamine-mediated acid secretion comparably. (Langtry, Grant, & Goa, 1989) Additionally, ranitidine and cimetidine have been shown to interfere with other drug metabolism when taken at the same time in humans, however, famotidine has been found to not have an effect on metabolism of those same drugs. (Langtry et al., 1989) Cimetidine has been shown to directly interfere with drugs metabolized through the cytochrome P450 system such as aminopyrine, antipyrine, diazepam, theophylline, phenytoin, and warfarin. (Humphries, 1987) Through human studies, famotidine has been shown to not interfere with the cytochrome P450 system when coadministered. (Humphries, 1987)

As shown in Table 3 the elimination half-life of famotidine reported in bovine and equine was longer than what was observed in goats during this study. (Balcomb et al., 2018) Total exposure to famotidine was higher in horses (Duran, 2003) than observed in the goats of this study. Goats could potentially metabolize the famotidine faster than bovine and equine species, which would attribute to the faster elimination. More rapid elimination of other gastroprotectants, such as pantoprazole, in goats when compared to cattle has also been observed. (Olivarez et al., 2020; Olivarez et al., 2022; Smith et al., 2021) The potential for more rapid elimination was one of the reasons for the increased dose used in this study compared to other investigations, as a higher exposure would result in increased likelihood of enough detectable concentrations for PK

modelling. The findings in this study are not suggestive of efficacy however, since the effective concentration and effective duration of therapy of famotidine in goats is currently unknown.

Adverse reactions that are commonly associated with famotidine in humans include dizziness, diarrhea, and headaches. (Howden & Tytgat, 1996) Some cardiovascular side effects have also been reported such as cardiac arrhythmias. (Duran, 2003) None of these adverse reactions were observed in the goats during this study, however cardiac monitoring was not performed.

Future studies regarding famotidine in goats include determining the pharmacokinetics of subcutaneous administration of famotidine. Another future study could investigate the pharmacodynamics which would help in determining how effective famotidine is in raising the pH of the abomasum. For these studies abomasal cannulation, as reported for pantoprazole and esomeprazole in ruminants could be utilized. (Olivarez et al., 2022; Smith et al., 2023) There have been studies in cats showing that the effects of famotidine diminish after multiple dosing. (Marks et al., 2018) An additional study could be designed to examine the pharmacokinetics and pharmacodynamics of multiple dosing for both intravenous and subcutaneous administration of famotidine in goats. Additional investigation could also evaluate famotidine administration in goats via nonlinear mixed-effects analysis. (Bon et al., 2018)

Limitations of this study include the sample size. Pharmacokinetic studies can adequately be supported with four to six animals, however, a larger sample size allows for more evaluation of variation within a population. Additionally, several gastroprotectant studies in ruminants have been conducted with fewer animals than in our study. (Balcomb et al., 2018; Fladung et al., 2022; Smith et al., 2023) The data generated in this study is compared to multiple other studies, some of which measured concentrations in serum instead of plasma. We were unable to find any studies comparing the concentrations of famotidine between the two matrices.

In conclusion, the elimination half-life of intravenously administered famotidine in goats appears to be lower than those reported in cattle and horses. (Balcomb et al., 2018; Duran, 2003) The area under the curve found in this study is also significantly less than what was reported in cattle, indicating less drug exposure, despite the higher dose administered to the study goats. (Balcomb et al., 2018) While the pharmacokinetic findings of famotidine in this study were lower than those reported in cattle and horses, this is not indicative of the efficacy. Future studies are needed to determine the effectiveness of famotidine as a treatment for abomasal ulceration in small ruminants.

5 Conflict of Interest

The authors state that the research conducted was in the absence of any commercial or financial relationships that could be construed as a possible conflict of interest.

6 Author Contributions

OE and JS developed experimental design. OE, JS, KC, BH, LH, and MH contributed to implementation of the study and animal health assessments. SC developed the analytical method for concentration determination. JS and OE performed pharmacokinetic analysis. All authors contributed to manuscript construction.

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8 Acknowledgments

The authors would like to thank Dr. Karen McCormick her assistance with goat procurement for this study.

9 Data Availability

All relevant data is presented within this manuscript.

Table 1: Pharmacokinetic parameters (mean \pm SD; geometric mean unless indicated) in goats after a single intravascular injection of 0.6 mg/kg famotidine (n=6)

Parameter	Unit	Mean (\pm SD)	Minimum	Maximum
C_0	ng/mL	5476.68 \pm 1530.51	3562.52	7203.35
AUC_{last}	min*ng/mL	54230.08 \pm 24947.6	36971.78	105263.5
$AUMC_{last}$	min ² *ng/mL	1076485 \pm 1549843	387565	4576760
MRT_{last}	min	19.85 \pm 12.14	9.38	43.48
λ_z	1/min	0.031 \pm 0.024	0.014	0.082
$T_{1/2\lambda_z}$ *	min	18.455 \pm 13.26	8.47	42
Cl	mL/min	441.87 \pm 187.35	236.01	773.2
V_z	mL/kg	321.924 \pm 221.667	141.652	609.82
V_{ss}	mL/kg	238.334 \pm 157.834	105.141	492.828

AUC_{last} : area under the curve to last measurable plasma concentration; $AUMC_{last}$: Area under the moments curve until last measurable plasma concentration ; C_0 : Plasma concentration immediately after intravenous administration; MRT_{last} : Mean residence time; λ_z : elimination rate; $T_{1/2\lambda_z}$: elimination half-life; Cl : clearance time; V_z : apparent volume of distribution; V_{ss} : steady state volume of distribution. *Harmonic mean

Figure 1: Concentration (ng/mL) versus time (min) after intravenous administration of famotidine (0.6 mg/kg)

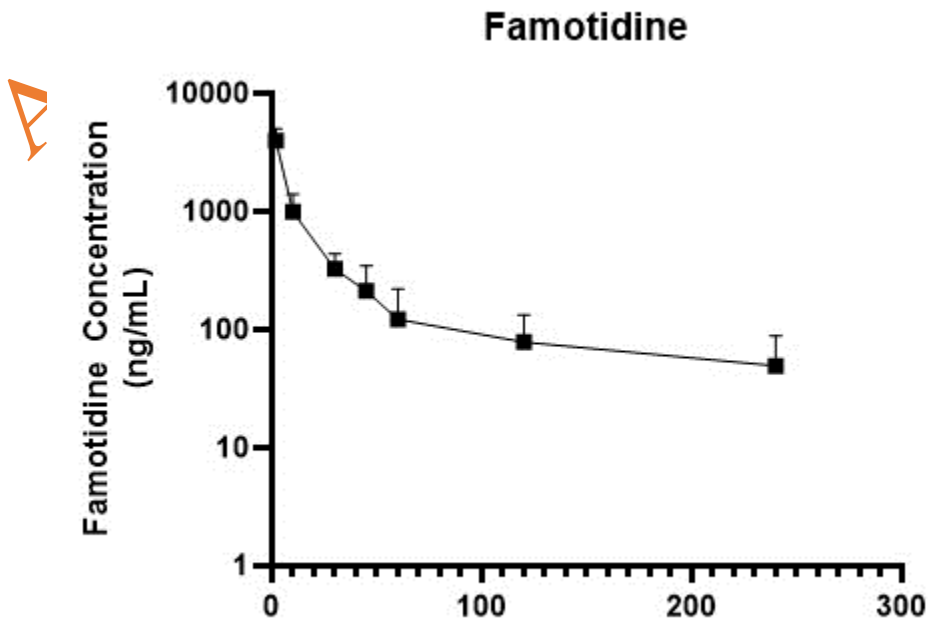


Table 2: Pharmacokinetic parameters (individual values) in goats following a single intravenous administration of 0.6 mg/kg famotidine (n = 6)

Parameter	Unit	Goat 1	Goat 2	Goat 3	Goat 4	Goat 5	Goat 6
C_0	ng/mL	6409.8	7151.51	5446.99	4211.28	7203.35	3562.52
Cl	mL/min	773.2	392.98	599.28	400.98	236.01	431.92
AUC_{last}	min*ng*mL	49764.3	105263.51	41332.49	36971.78	63365.35	50145.52
$AUMC_{last}$	min ² *ng/mL	867380	4576760	387565	665805	1043915	1455205
MRT_{last}	min	17.43	43.48	9.38	18.01	16.47	29.02
λ_z	1/min	0.035	0.016	0.082	0.037	0.037	0.018
$T_{1/2\lambda_z}$	min	19.54	42	8.47	18.88	18.6	39.48
V_{ss}	mL/kg	258.67	296.88	141.99	339.84	183.59	415.02
V_z	mL/kg	327.32	330.75	176.09	429.93	247.34	664.95

AUC_{last} : area under the curve to last measurable plasma concentration; $AUMC_{last}$: Area under the moments curve to last measurable plasma concentration; C_0 : Plasma concentration immediately after intravenous administration; MRT_{last} : Mean residence time; λ_z : elimination rate; $T_{1/2\lambda_z}$: elimination half-life; Cl : clearance time; V_z : apparent volume of distribution; V_{ss} : steady state volume of distribution. *Harmonic mean

Table 3: Comparative pharmacokinetics of famotidine after intravenous administration in several species

Species	Dose (mg/kg)	C_{max} (ng/mL)	Elimination half-life (min)	AUC (ng*min/mL)	Reference	Serum or Plasma
Bovine	0.4	N/A	199.8	421,140	Balcomb et al., 2018	Serum
Equine	0.5	N/A	127.02		Duran, 2003	Plasma
Goat	0.6	5476.68	18.455	54,230.08	Present Study	Plasma

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