

## Metabolic profile and ruminal and abomasal pH in sheep subjected to intravenous ranitidine<sup>1</sup>

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**ABSTRACT.**- Morgado A.A., Nunes G.R., Martins A.S., Hagen S.C.F., Rodrigues P.H.M. & Sucupira M.C.A. 2014. **Metabolic profile and ruminal and abomasal pH in sheep subjected to intravenous ranitidine.** *Pesquisa Veterinária Brasileira* 34(Supl.1):17-22. Departamento de Clínica Médica, Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, Av. Prof. Dr. Orlando Marques de Paiva 87, São Paulo, SP 05508 270, Brazil. E-mail: [aline.morgado@usp.br](mailto:aline.morgado@usp.br)

Brazilian sheep production has intensified, predisposing sheep to an increased incidence of digestive disorders, such as abomasal ulcers. Ranitidine is used to prevent and treat this disease; however, there is little information on the parenteral use of this drug in adult ruminants. Few data exist on the concomitant metabolic changes and the behavior of the digestive system associated with its use. For this study, five healthy male sheep with ruminal and abomasal cannulas were used. A 5x5 Latin square experiment with a 2x2+1 factorial arrangement of the treatments was performed. Sheep treated with drug doses of 1 or 2mg/kg ranitidine administered intravenously every 8 or 12 hours were compared with the control group, was treated intravenously with 1 mL of physiological solution per 25 kg every 12 hours. Higher total protein concentrations, hemoglobin levels, as well as increased aspartate aminotransferase activity and increased abomasal pH for up to 150 min following drug administration were observed in all animals that received the drug, regardless of dose and frequency. The animals treated every 12 hours showed a decrease in leukocyte number compared with the control group and with the animals treated every 8 hours. Increased serum creatinine concentrations were observed in the animals treated every 8 hours. Treatments of 1mg/kg every 8 hours and 2mg/kg every 12 hours increased the red blood cell count and decreased the serum pepsinogen. All protocols studied were safe for healthy sheep, but 1mg/kg ranitidine every 8 hours and 2mg/kg ranitidine every 12 hours were the most effective protocols for gastric protection.

INDEX TERMS: Metabolic profile, ruminal pH, abomasal pH, sheep, ranitidine, biochemistry profile, H<sub>2</sub> antagonists, hydrogen ion concentration, ruminants.

**RESUMO.**- [Perfil metabólico ruminal e pH abomasal em ovinos tratados com ranitidina por via intravenosa.] A ovinocultura brasileira tem se intensificado, o que

predispõe os animais à maior incidência de transtornos digestivos, como a úlcera de abomaso. A ranitidina é utilizada na prevenção e tratamento desta afecção, no entanto há pouca informação sobre a indicação parenteral deste fármaco para ruminantes adultos. São escassas as informações a respeito das alterações metabólicas e do comportamento do sistema digestório associados ao seu uso. Para este estudo foram utilizados cinco ovinos, machos, hígidos, providos de cânula ruminal e abomasal. O delineamento foi Quadrado Latino 5x5 com arranjo fatorial de tratamentos 2x2+1. Os ovinos tratados com as doses de 1 e 2mg/kg de ranitidina administrada por via intravenosa a cada 8 ou 12 horas foram comparados aos animais do grupo controle,

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tratados por via intravenosa com 1mL de solução fisiológica por 25 kg a cada 12 horas. Maiores concentrações de proteína total e hemoglobina, maiores atividades de AST e aumento do pH abomasal por até 150 minutos foram observados em todos os animais que receberam o fármaco, independentemente de dose e frequência. Os animais tratados a cada 12 horas mostraram diminuição do número de leucócitos comparados aos animais tratados a cada 8 horas e aos animais do grupo controle. Observou-se aumento das concentrações de creatinina nos animais tratados a cada 8 horas. Os tratamentos 1mg/kg a cada 8 horas e 2mg/kg a cada 12 horas aumentaram o número de hemácias e diminuíram as concentrações séricas de pepsinogênio. Todos os protocolos estudados foram seguros para ovinos saudáveis, porém 1mg/kg de ranitidina a cada 8 horas e 2mg/kg a cada 12 horas mostraram-se mais eficientes quanto à proteção gástrica.

**TERMOS DE INDEXAÇÃO:** Perfil metabólico ruminal, pH abomasal, ovinos, ranitidina, perfil bioquímico, antagonistas H<sub>2</sub>, concentração hidrogeniônica, ruminantes.

## INTRODUCTION

Abomasal ulcers constitute a multifactorial disease that results from an imbalance of the gastric mucosa defense mechanisms. Pepsin excess, direct trauma, abomasal distension, the prolonged use of non-steroidal anti-inflammatory drugs, stress, and hyperacidity can all trigger abomasal ulcers (Ogilvie 2005, Borges & Moscardini 2007, Fecteau & Whitlock 2009). Although the economic losses caused by this disease have not been quantified, it is known that decreases in dry matter intake and productive performance are among its consequences (Mills Wallace et al. 1994, Radostits et al. 2002).

The treatment for abomasal ulcers requires the reduction of gastric acid secretion, which can be achieved using reversible histaminergic type H<sub>2</sub> blockers (Mills Wallace et al. 1994), which include ranitidine, cimetidine, famotidine, and nizatidine (Boothe 2003, Guard 2006).

Cimetidine and ranitidine are the most commonly used for treatment of abomasal ulcers. Ranitidine has longer action than cimetidine as well as lower influence on hepatic blood flow and on the metabolism of other drugs (Grant et al. 1989, Boothe 2003, Romich 2005, Xavier et al. 2011).

Most studies testing ranitidine in ruminants have been performed in calves (Fubini & Divers 2008, Fecteau & Whitlock 2009). The few studies that tested this drug in adult ruminants used high doses, such as 15 and 45mg/kg of body weight of ranitidine, administered intravenously (IV) and orally, respectively, to reduce abomasal acidity in sheep (Dowling 1995).

Therefore, we evaluated the effects of the intravenous administration of 1 and 2mg of ranitidine per kilogram of body weight given every 12 or 8 hours in adult sheep.

## MATERIALS AND METHODS

This study was approved by the Ethics Committee of the Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo (protocol 2271/2011).

Five adult sheep, crossbred and healthy, with an average body weight of 45 kg, and fitted with ruminal and abomasal cannulas, were housed in individual cages with individual feeders and water bowls throughout the experiment. The sheep's diet consisted of hay and commercial concentrate in an 80:20 ratio, with a total daily dry matter intake of 2.75% of body weight. Food was provided twice daily at 6:30 a.m. and 6:30 p.m., and water was consumed ad libitum.

The experimental design consisted of a 5x5 Latin square with a 2x2+1 factorial arrangement of treatments. The factors considered were ranitidine doses of 1 and 2mg/kg administered twice daily (every 12 hours) and three times a day (every 8 hours). The combinations of each dose with each frequency were compared with the control treatment (1 mL of saline solution/25 kg every 12 hours).

Each experimental period consisted of 21 days. During the first 14 days the animals were rested in order to eliminate any possible residual effect of the previous treatment ("wash out"). From day 15 to 21, the animals received the drug according to established protocol and data were collected.

On the 18th day of each period, paired samples of ruminal fluid, abomasal fluid, and blood were collected at 6 a.m., 9 a.m., 11 a.m., 1 p.m., 3 p.m., 5 p.m., and 7 p.m. The animals received their second meal immediately after the last collection. On the 20<sup>th</sup> day, fecal samples were collected, processed, and evaluated using the commercial kit Hemoplus (code 1031; Newprov, Pinhais, Paraná, Brazil). On day 21, the clinical parameters of each sheep were assessed.

Ruminal and abomasal fluids were obtained through the cannulas, and the pH was determined immediately after collection using a digital potentiometer.

Blood samples were collected by jugular vein puncture to obtain whole blood, plasma, and serum. The concentrations of serum pepsinogen (Paynter 1992), fibrinogen (Schalm, Jain & Carroll 1981), packed cell volume, and blood count (automated haematology counter ABC Vet, ABX, Gurnee, Illinois, USA) were determined. The differential leukocyte count was obtained by evaluation of a blood smear.

The serum concentrations of urea (kit UR3825), creatinine (kit CR3814), albumin (kit AB3800), total protein (kit TP4001), and total calcium (kit CA3871); plasma glucose levels (kit GL3815); and the activities of serum aspartate aminotransferase (AST) (kit AS3804), gamma-glutamyl transferase (GGT) (kit GT3817), and creatine kinase (CK) (kit CK110) were determined using Randox kits with an automatic biochemical analyzer (RX Daytona, Randox, Crumlin, County Antrim, United Kingdom).

The data were analyzed with the Statistical Analysis System (SAS, Version 9.3, 2010) using a MIXED procedure. First, the normality of the residuals was verified using the Shapiro-Wilk test, and "outliers" were identified using the UNIVARIATE procedure of SAS.

The data that did not meet the normality assumption regarding their residues were subjected to logarithmic or square root transformation. All data were subjected to variance analysis using a Latin square design with a 5x5 factorial arrangement of treatments (2x2+1).

The model assumed treatment as a fixed effect and animal and period as random effect. Repeated measures were used for ruminal and abomasal pH and serum pepsinogen determinations. In these cases, the treatment effect, time point effect, and time point\*treatment interaction were included in the model as fixed effects. The animal and period effects, as well as the animal\*time point and period\*time point interactions, were treated as random effects.

The treatment effect was analyzed using orthogonal contrasts

and decomposed as follows: 1) control versus all treated groups, 2) dose effect, 3) frequency effect, and 4) interaction between dose and frequency. A significance level of 5% was used for all tests.

## RESULTS

The mean urea, creatinine, albumin, total protein, glucose, total calcium, sodium, potassium, and chlorine concentrations, as well as AST, GGT, and CK activities, are shown in Table 1.

The administration of 2mg/kg of ranitidine increased the serum urea values and decreased glycemia regardless of frequency. When administered every 8 hours, ranitidine increased the creatinine concentrations. Ranitidine also increased the serum levels of total protein and stimulated AST activity regardless of the dose and frequency of administration.

The complete blood count and fibrinogen concentration results are shown in Table 2. An interaction was identified for the red blood cell count. Increased numbers of red blood cells were observed with 1mg/kg of ranitidine administered every 8 hours or 2mg/kg administered every 12 hours. The control group had lower red blood cell levels than the treated animals. Ranitidine, regardless of dose and frequency, increased the hemoglobin concentration. Fewer leukocytes were observed with ranitidine treatment, occurring a greater reduction with the administration every 12 hours than every 8 hours.

Ranitidine administration showed no effect on measured clinical parameters (Table 3).

Figure 1 presents the abomasal pH results at 6, 9, 11 a.m. and 1, 3, 5, 7 p.m. There were significant treatment\*time point interactions). Ranitidine administration influenced the abomasal pH at 9 a.m. and at 1 p.m. A dose effect was

**Table 1. Serum biochemical values (mean (sd)) of healthy sheep treated with different ranitidine protocols**

Variable	Treatments				Probability of				
	Every 12 hours		Every 8 hours		orthogonal contrasts				
	Control	1mg/kg	2mg/kg	1mg/kg	2mg/kg	C vs. T	D	F	D*F
Urea, mmol/L	5.85 (1.93)	6.20 (0.99)	6.76 (1.21)	6.06 (1.11)	6.87 (1.20)	NS	0.0084	NS	NS
Creatinine, µmol/L	81.3 (14.9)	81.3 (6.5)	82.0 (3.8)	88.6 (7.8)	89.5 (5.8)	NS	NS	0.0350	NS
Albumin, g/L	30.3 (2.6)	31.4 (1.5)	31.8 (1.5)	31.6 (0.9)	30.8 (1.3)	NS	NS	NS	NS
TP, g/L	69.8 (6.6)	73.4 (4.3)	74.7 (6.7)	74.7 (5.8)	74.5 (7.5)	0.0109	NS	NS	NS
Glucose, mmol/L	3.74 (0.48)	3.82 (1.04)	3.36 (0.32)	3.68 (0.28)	3.49 (0.38)	NS	0.0298	NS	NS
AST, U/L at 25°C	70.2 (9.7)	84.2 (18.6)	77.2 (14.5)	89.3 (11.0)	80.3 (12.8)	0.0407	NS	NS	NS
GGT, U/L at 25°C	28.9 (5.1)	28.6 (5.4)	29.0 (7.4)	27.1 (4.7)	27.5 (6.6)	NS	NS	NS	NS
CK, U/L at 25°C	75.3 (19.2)	81.5 (19.2)	89.3 (25.9)	76.9 (19.1)	82.9 (23.6)	NS	NS	NS	NS

Blood samples were collected on the 4<sup>th</sup> day of treatment; *sd* = standard deviation, C vs. T = Control vs. treated, D = dose, F = frequency, D\*F = dose x frequency interaction, NS = not significant, TP = total protein, AST = aspartate aminotransferase enzyme, GGT = gamma-glutamyl transferase enzyme, CK = creatine kinase enzyme.

**Table 2. Haematological values (mean (sd)) of healthy sheep treated with different ranitidine protocols**

Variable	Treatments				Probability of				
	Every 12 hours		Every 8 hours		orthogonal contrasts				
	Control	1mg/kg	2mg/kg	1mg/kg	2mg/kg	C vs. T	D	F	D*F
PCV, %	29.5 (4.2)	31.0 (3.5)	32.2 (3.1)	31.6 (2.8)	29.4 (3.2)	NS	NS	NS	NS
RBC, 10 <sup>12</sup> /L	6.91 (0.58)	7.35 (0.56)	7.72 (0.63)	7.64 (0.99)	7.16 (0.82)	0.0041	NS	NS	0.0056
Hemoglobin, g/dL	9.7 (0.5)	10.7 (1.3)	11.3 (0.5)	10.5 (1.7)	9.9 (1.1)	0.0167	NS	NS	NS
Leukocytes, 10 <sup>9</sup> /L	8.65 (4.07)	5.90 (1.15)	6.22 (1.70)	7.08 (1.59)	7.58 (1.40)	0.0172	NS	0.0426	NS
Neutrophils, 10 <sup>9</sup> /L	3.25 (1.66)	2.75 (8.88)	3.61 (1.57)	3.55 (1.59)	4.13 (1.82)	NS	NS	NS	NS
Lymphocytes, 10 <sup>9</sup> /L	3.35 (1.94)	2.93 (7.49)	2.50 (1.12)	3.90 (1.61)	3.05 (8.40)	NS	NS	NS	NS
Monocytes, 10 <sup>9</sup> /L	0.05 (0.06)	0.13 (0.13)	0.12 (0.17)	0.06 (0.08)	0.11 (0.16)	NS	NS	NS	NS
Eosinophils, 10 <sup>9</sup> /L	0.33 (0.57)	0.10 (0.09)	0.04 (0.05)	0.15 (0.21)	0.29 (0.60)	NS	NS	NS	NS
Platelets, 10 <sup>9</sup> /L	176.3 (67.5)	165.2 (62.2)	187.0 (52.1)	201.0 (67.6)	189.4 (98.6)	NS	NS	NS	NS
Fibrinogen, g/L	3.50 (1.73)	2.25 (0.50)	2.20 (0.45)	3.50 (0.57)	2.50 (1.00)	NS	NS	NS	NS

Blood samples were collected on the 4<sup>th</sup> day of treatment *sd* = standard deviation, C vs. T = Control vs. treated, D = dose, F = frequency, D\*F = dose x frequency interaction, NS = not significant, PCV = packed cell volume, RBC = red blood cell.

**Table 3. Clinical parameters of healthy sheep treated with different ranitidine protocols**

Variable	Treatments				Probability of						
	Every 12 hours		Every 8 hours		orthogonal contrasts						
	Control	1mg/2mg/kg	1mg/kg	2mg/kg	$\bar{x}$	<i>sd</i>	C vs. T	D	F	D*F	
Cardiac freq., bpm	78	84	90	82	83	84	14	NS	NS	NS	NS
Resp freq., breaths/min	13	14	14	15	14	14	3	NS	NS	NS	NS
Ruminal movements in 3 min	3	3	3	3	3	3	1	NS	NS	NS	NS
Temperature, °C	38.4	38.3	38.8	38.3	38.2	38.4	0.9	NS	NS	NS	NS

Clinical parameters were collected on the 7<sup>th</sup> day of treatment,  $\bar{x}$  = mean of all treatments (including control), *sd* = standard deviation of all treatments (including control), C vs. T = Control vs. treated, D = dose, F = frequency, D\*F = dose x frequency interaction, bpm = beats per minute, NS = not significant.

found at 9 a.m., with the 2mg/kg groups exhibiting higher values than the control group. There was also a frequency effect, wherein the groups treated every 12 hours exhibited higher pH values than the control group. At 1 p.m. an increase of pH values was observed regardless of dose or frequency. At 3 p.m. and 5 p.m., the pH values were higher in the groups treated every 8 hours than in the control group, whereas at 7 p.m. the pH values were higher in the animals treated every 12 hours than in the control group. The ruminal pH showed general media of 6.58 and standard deviation of 0.29, with no significant effects.

Figure 2 shows the serum pepsinogen values at 6, 9, 11 a.m. and 1, 3, 5, 7 p.m. The serum pepsinogen concentration

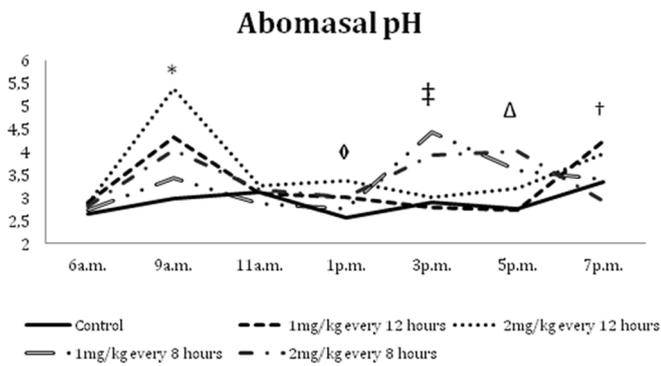


Fig.1. Note: Treatment\*time point interactions ( $P=0.0007$ ). \* Control vs ranitidine treatment ( $P=0.0051$ ), dose effect (2mg/kg of ranitidine higher than 1mg/kg of ranitidine and control group) ( $P=0.0282$ ) and frequency effect (every 12 hours higher than every 8 hours and control group) ( $P=0.0070$ ).  $\diamond$  Control vs ranitidine treatment (regardless of dose or frequency effect) ( $P=0.0211$ ).  $\ddagger$  Frequency effect (every 8 hours higher than every 12 hours and control group) ( $P=0.0009$ );  $\Delta$  Frequency effect (every 8 hours higher than every 12 hours and control group) ( $P=0.0033$ );  $\dagger$  Frequency effect (every 12 hours higher than every 8 hours and control group) ( $P=0.0227$ ).

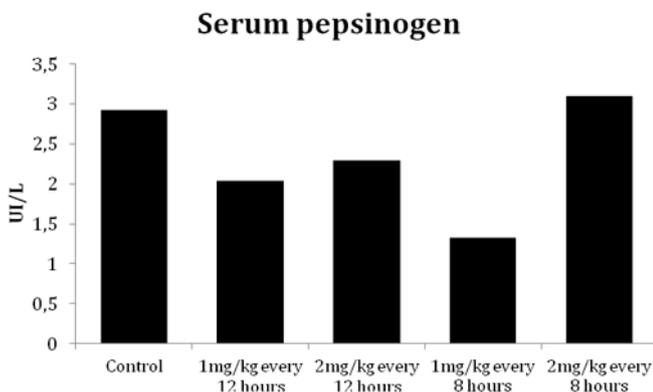


Fig. 2. Note: There was dose x frequency interaction ( $P = 0,0380$ ).

always was in normal range however with 1mg/kg every 8 hours we observed the lowest value.

The fecal occult blood test was negative in all cases.

## DISCUSSION

All ranitidine protocols used in this study increased the total serum protein levels, although all values remained in the normal range for sheep (60-79g/L) (Kaneko et al. 2008). As the concentration of albumin was not influenced by ranitidine, we can infer that the total protein increase was due to the increased globulin concentration.

Prior research revealing the action of histamine H<sub>2</sub>-antagonist in the prevention of such histamine effects as the immune response suppression of antigens, T cell cytotoxic activity, immunoglobulin synthesis, and lymphokine production explains the observed total protein increase (Hosseinfard et al. 2013). The globulin profile was not determined in this study but should be evaluated in future studies.

Sheep treated with ranitidine every 12 hours, regardless of the dose, had lower levels of leukocytes, although the levels were within the normal range. The same effect was observed in human duodenal ulcers treated with 150mg of ranitidine every 12 hours for 2 weeks (Hrycek et al. 1994) and in rats treated with a single dose of 100mg/kg (Malfara et al. 2005). In the human study, few leukocytes were found, but they showed greater phagocytic activity than before treatment (Hrycek et al. 1994). The similar finding of few leukocytes in our study warrants future studies on the effects of ranitidine administration on immunity and/or inflammatory effects in ruminants.

Ranitidine administration elevated the hemoglobin serum concentrations regardless of dose and frequency, but all values were within the normal range for sheep (9-14g/dL) (Kaneko, Harvey & Bruss 2008). Hemoglobin type was not determined in this study, but it has been reported that ranitidine leads to methemoglobin formation in rats, suggesting that this drug is an inductor of this process (Malfara et al. 2005). If the sheep in this study had increased methemoglobin formation, it must have been small because no change in the respiratory rate or mucous membrane color of the animals was detected.

Ranitidine administration at doses of 1mg/kg every 8 hours and 2mg/kg every 12 hours increased the red blood cell count in sheep. This result is quite different from those mentioned in literature, as several studies reported negative effects of ranitidine on hematopoiesis. Thrombocytopenia, granulocytopenia, and hemolytic anemia have all been reported in rats receiving intraperitoneal ranitidine (Malfara et al. 2005), and thrombocytopenia has been reported in humans treated with this drug (Spychal & Wickham 1985, Amos et al. 1987). A review states that thrombocytopenia caused by H<sub>2</sub>-antagonist use was attributed to the direct suppression of bone marrow combined with the development of antibodies against platelets (Wade et al. 2002). However, the same authors found no direct relationship between H<sub>2</sub>-antagonists and thrombocytopenia and stressed that this effect was observed only when other risk factors appeared, such as sepsis or gastrointestinal bleeding.

All of the ranitidine protocols tested were able to increase AST activity in sheep, but this activity was always within the normal range (60-280 U/L) (Kaneko et al. 2008) and returned to baseline values during the rest period ("washout"). Clinical trials with ranitidine in humans also showed a transient increase in transaminase activities and some cases of mild hepatitis, but interruption of the treatment resolved these problems (Fisher & Le Couteur 2001).

The observed changes in urea and creatinine concentrations were in normal range. Some high values could not be associated to clinical manifestations.

Ranitidine was administered continuously for seven days and that the biochemical parameters were determined on the fourth day of each period of administration. Additional studies with longer drug administration periods are suggested, although only stool softening was observed as an adverse effect in Beagle dogs treated orally for seven

years with 50mg/kg ranitidine once a day and dogs receiving 5mg/kg ranitidine orally twice a day for the same period, showed no adverse effects (Spurling et al. 1989).

Although within the normal range, there was a decrease in serum glucose when 2mg/kg of ranitidine was administered, regardless of the administration frequency. This decrease has not been described. This reduction may be a result of high metabolic activity, because sheep treated with 2mg of ranitidine/kg showed higher AST activity and urea concentrations than the other groups.

The biochemical parameters showed variations of small magnitude in the sheep receiving ranitidine. These changes had little clinical significance, as the animals were healthy and these variables remained within normal limits. The evaluation of the drug in adult ruminants with abomasal ulcers should be done in order to study the drug effect in clinical conditions.

The reduced production of hydrochloric acid can be detected by the increased pH of the gastric fluid. The effect of ranitidine on abomasal pH was observed up to 150 minutes after administration, regardless of the dose and frequency used. An increase in the abomasal pH was observed for 24 to 48 hours following a single intravenous ranitidine administration of 15mg/kg to fasted sheep (Duran et al. 2007). Nevertheless, steers treated intramuscularly with 6.6 mg/kg of ranitidine showed an increase in abomasal pH only up to 60 minutes (Milss Wallace et al. 1994) and the authors indicated the need for more frequent ranitidine administration in ruminants than in non ruminant species species.

It has long been known that interrupting the release of hydrochloric acid is important for healing gastric ulcers (Milss Wallace et al. 1994), being the pH increase of the abomasal fluid indicative of effectiveness of the ulcer treatment (Ahmed et al. 2001, Christensen et al. 2001). No studies with adult ruminants affected by abomasal ulcers were performed. Thus, further studies should be conducted to verify the influence of the increased abomasal pH resulting from the use of H<sub>2</sub>-receptor antagonists on abomasal ulcer healing.

The ruminal pH was not altered by the drug, and its values remained in their optimal range at all times. Furthermore, no changes in vital parameters were observed with any protocol studied, demonstrating that ranitidine use for up to one week did not affect the health of healthy animals.

The serum pepsinogen concentration can justify the benefit of ranitidine administration. Pepsinogen is the inactive form of pepsin, and it is converted to pepsin in an acid environment. The conversion begins at a gastric pH of approximately 5.0, and its optimal activity occurs at pH values between 1.8 and 3.5 (Argenzio 2006). A high serum pepsinogen level is a good indicator of abomasal mucosa lesions, and animals with abomasal ulcers have higher pepsinogen concentrations than healthy animals. The normal serum values range from 0 to 5.0 IU/L (Mesarič 2005). The lower concentration observed in the group receiving 1mg/kg every 8 hours suggest a benefit of the use of ranitidine in abomasal ulcer treatment.

## CONCLUSION

Administration of ranitidine regardless of the protocols studied demonstrated to be safe for healthy sheep. In addition 1mg/kg every 8 hours and 2mg/kg every 12 hours of ranitidine administered intravenously for 1 week were the most effective protocols for the reduction of abomasal pH.

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