

# Effects of prolonged use of meloxicam in healthy horses: clinical, laboratory, gastroscopic, and electrocardiographic findings

## Efeitos do uso prolongado de meloxicam em equinos hígidos: achados clínicos, laboratoriais, gastroscópicos e eletrocardiográficos

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### Highlights

No relevant adverse changes were observed in the experimental animals.  
Discreet lesions were observed in the squamous gastric mucosa on day 14.  
There were no clinical changes in any of the horses during the experiment.

### Abstract

Non-steroidal anti-inflammatory drugs are extensively used in veterinary practice. COX-2 inhibitors are considered to be safer than non-selective inhibitors; however, there are few studies address of their long-term use in equine species. The goal of this study was to identify the possible adverse effects of meloxicam (a preferential COX-2 inhibitor) in healthy horses, administered at a dose of 0.6 mg/kg, orally, once a day, for 28 days. A paired test was performed with seven animals, and the clinical, hematological, biochemical, and gastroscopic parameters, as well as bleeding time, were evaluated in five timepoints and an electrocardiogram at three timepoints. No relevant adverse effects were observed in terms of the parameters evaluated. Significant differences were found in heart rate, AST and P wave duration, segmented neutrophils (%), and the levels of erythrocytes, hemoglobin, hematocrit, and MCH, compared with these parameters at T0; however, no animal manifested clinical alterations. Gastroscopy revealed discrete lesions (Grade 1) in the squamous gastric mucosa on day 14 of treatment in all animals;

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however, at the end of the study (day 28) these lesions had regressed to grade 0 in three of the horses and remained at grade 1 in the other four animals. Based on these results, we conclude that the use of meloxicam at a daily dose of 0.6 mg/kg, orally, for 28 consecutive days, did not cause relevant adverse effects in healthy horses.

**Key words:** Adverse effect. Anti-inflammatory. Electrocardiogram. Gastroscopy. Equine.

## Resumo

Os anti-inflamatórios não esteroides são amplamente utilizados na prática veterinária e os inibidores da COX-2 são propostos como mais seguros que os inibidores não seletivos, porém, poucos estudos abordam seu uso por tempo prolongado na espécie equina. Este estudo teve como objetivo identificar os possíveis efeitos adversos do uso de meloxicam (inibidor preferencial da COX-2) em equinos hígidos, na dose de 0,6 mg/kg, por via oral, uma vez ao dia, durante 28 dias. Um teste pareado foi realizado com sete animais e os parâmetros clínicos, hematológicos, bioquímicos, tempo de sangramento e gastroscópicos foram avaliados em cinco momentos e eletrocardiograma em três. Não foram observados efeitos adversos relevantes nos parâmetros avaliados. As variáveis frequência cardíaca, eritrócitos, hemoglobina, hematócrito, HCM, neutrófilos segmentados, AST e duração da onda P apresentaram diferença significativa em relação ao T0, porém nenhum animal manifestou alterações clínicas. Na gastroscopia foram observadas lesões discretas (grau 1) na mucosa gástrica escamosa no dia 14 de tratamento em todos os animais, porém, ao final do estudo (dia 28) essas lesões regrediram para grau 0 em três pacientes e permaneceram em grau 1 em quatro animais. O uso de meloxicam na dose diária de 0,6mg/kg, por via oral, durante 28 dias consecutivos, não causou efeitos adversos relevantes em cavalos hígidos.

**Palavras-chave:** Efeito adverso. Anti-inflamatório. Eletrocardiograma. Gastroscopia. Equino.

## Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in the clinical routine of physicians and veterinarians for their anti-inflammatory and analgesic effects. Treatment with non-selective NSAIDs can cause considerable adverse effects, mainly related to renal toxicity, gastric lesions, and right dorsal colitis. COX-2 inhibitors (coxibs) are considered safer alternative, with reduced adverse effects compared to non-selective NSAIDs (Van Galen et al., 2021).

4-hydroxy-2-methyl- N - (5-methyl-2-thiazolyl) -2 H -1,2- benzothiazin-3-carboxamide-1,1-dioxide is an oxicam

derivative of the enolic group of NSAIDs and a preferential COX-2 inhibitor (Brideau et al., 2001). Meloxicam is widely used by veterinarians for the treatment and control of pain and inflammation in horses (D. A. Santos et al., 2020).

Despite the lack of definitive clinical data on the use of meloxicam, there is a perception among veterinarians that preferential COX-2 compounds have a good safety profile, and this consideration influences therapeutic decisions (Vivancos et al., 2015). However, further investigations into the long-term use of coxibs and their adverse effects are needed.

In this study we aimed to determine whether there are adverse effects caused by the use of meloxicam, at a dose of 0.6 mg/kg, orally, once daily (SID), for 28 consecutive days, based on bleeding time and clinical, hematological, biochemical, gastroscopic, and electrocardiographic parameters in healthy horses.

## Materials and Methods

### *Animals*

Seven healthy adult horses of mixed breeds, four females and three males, were the subjects of this study. The animals, ranging in age from 4 to 10 years, belong to the farm school of the Federal University of Alagoas (UFAL), Viçosa Campus. The animals were already adapted to the place where the study was carried out. During the experimental period, the horses were kept in enclosures that allowed them to be observed during the evaluation period. Commercial maintenance feed (12% crude protein), measured out as 1% of body weight, provided twice a day, as well as Tifton hay (*Cynodon* spp.) and water ad libitum. The horses roamed freely in paddocks during the day and were only stabled on the nights before the examinations, to perform the necessary fasting. All the animals were considered healthy based on clinical history, physical examination, hematology, serum biochemistry, and previous gastroscopic examination. The horses were tested for equine infectious anemia and glanders, with negative results, and were dewormed with ivermectin 30 days before the start of the study.

### *Ethics committee*

The project was approved by the Ethics Committee on Animal Use of the Federal University of Alagoas (CEUA/UFAL), under number 016/2018, and was performed in accordance with the national guidelines for research animals.

### *Experimental protocol*

A paired test was conducted, and the data collected prior to treatment (at T0), were used as controls against which to evaluate treatment effects at subsequent timepoints. For the clinical evaluation, laboratory tests, bleeding time, and gastroscopic variables, the horses were evaluated at five timepoints: 24 h prior to the administration of the drug (T0) and at 7 (T7), 14 (T14), 21 (T21) and 28 days (T28) following the start of treatment. For evaluation of the electrocardiogram, the animals were evaluated at three timepoints (T0, T14, and T28). The animals were given meloxicam, orally, at a dose of 0.6 mg/kg, once a day, in the morning, for 28 consecutive days. The dosage was based on each animal's weight at the beginning of the study. The formulation of meloxicam was prepared in a veterinary compounding pharmacy (Drogavet®) in the form of an oral paste, with a specific dosing syringe labeled for each horse. The clinical examinations and collection of material for laboratory tests, as well as the electrocardiogram and gastroscopy examinations, were all performed in the morning (between 08:00 and 10:00), and after that, the drug was administered.

### *Clinical evaluation*

The following indicators were evaluated, according to the clinical examination described by Speirs (1999): level of consciousness, posture, appetite, heart rate (HR) and respiratory rate (RR), intestinal motility, body temperature, mucosal coloration, capillary refill time (CRT) and body weight, with respect to the HR, RR, temperature, CRT and weight variables, the non-parametric Kruskal-Wallis test was performed to compare the data collected at different timepoints, adopting a 5% significance level (given that the variables did not meet the normality assumptions) when verified by the Shapiro Wilk test, reaching a significance of less than 5%. Statistical analyses were performed using SAS 9.2 software (SAS Inst., Inc., Cary, NC).

### *Laboratory analysis and bleeding time test*

After antisepsis, 5-mL blood samples were collected through jugular venipuncture in vacuum tubes with EDTA, to perform a hemogram, including erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, leukocytes, segmented neutrophils, lymphocytes, eosinophils, monocytes, platelets, fibrinogen, and total plasma protein (Kerr, 2003). As well, 10-mL blood samples were collected in vacuum tubes with gel for serum separation, to perform serum biochemistry. The hemograms were carried out in an automatic device (Hematoclin 2.8 Vet / Bioclin) by the impedance method. The evaluation of the *in vivo* bleeding time was performed according to the technique described by Kerr (2003), in the oral mucosa, and the time elapsed from the

beginning to the end of the bleeding was timed. The biochemical variables (glucose, AST, CK, GGT, albumin, urea, alkaline phosphatase, creatinine) were performed in an automatic biochemical analyzer (SX-160, Sinnova) and specific kits for each enzyme. The level of C-reactive protein (CRP) was determined via the ultra-sensitive turbidimetric immunoassay technique in Siemens Dimensions (automated clinical chemistry analyzer), model RXL, with test kits from the same company. Applying the Shapiro-Wilk normality test ( $p > 0.05$ ), it was verified that the data presented a normal distribution; therefore, the contrast between the means of laboratory tests and bleeding time were evaluated by means of analysis of variance (ANOVA) with the application of the Bonferroni test, verifying the contrast between the means of the data collected at T0 and at the other timepoints, adopting the significance level of 5%. Statistical analyses were performed using SAS 9.2 software (SAS Inst., Inc., Cary, NC). All values regarding laboratory tests were compared with the reference values for equine species according to Kaneko et al. (2008).

### *Gastroscopic evaluation*

A gastroscopic examination was performed in order to evaluate the effects of anti-inflammatory drugs on the gastric mucosa of the treated animals. All animals were fasted for 18 h (bulk feed) and were not given access to water for 8 h prior to the examination. As sedation was necessary for the tests and to avoid its interference with the other variables, the gastroscopic evaluation was performed after the measurement of all other parameters. The animals were sedated

with detomidine, at a dose of 0.02 mg/kg by intravenous route and, when necessary, a nose twitch was used to avoid abrupt head movements. A colono-fiberscope, 300 cm long and 12.5 mm in diameter, was used together with the video endoscopy and image reproduction apparatus. The colono-fiberscope was washed between each gastroscopic examination and after the end of the examinations, using Endosime AW<sup>®</sup> plus solution diluted in distilled water at a ratio of 2.0 mL of Endosime AW<sup>®</sup> plus to 500 mL of distilled water, followed by repeated rinsing with distilled water. After cleaning, the device was dried using compressed air. Gastroscopic findings were classified according to the "Consensus Statement of the European College of Equine Internal Medicine for Gastric Ulcer Syndrome in Adult Horses", which recognizes the terminology equine gastric ulcer syndrome (EGUS) as a general and comprehensive term to describe erosive and stomach ulcers and equine squamous gastric disease (ESGD) and equine gastric glandular disease (EGGD) as terms that more specifically describe the affected anatomical region. With respect to ESGD, the lesions are evaluated according to degrees of severity (G): G0: intact epithelium and no appearance of hyperkeratosis; G1: mucosa is intact, but there are areas of hyperemia and/or hyperkeratosis; G2: small, single or multifocal lesions; G3: large single or extensive superficial lesions; and G4: extensive lesions with areas of apparent deep ulceration. As for EGGD, lesions are described according to their anatomical location (cardia, fundus, antrum, and pylorus), distribution and appearance (focal, multifocal, diffuse; mild, moderate, severe; flat and dried using compressed air, flat and fibrinosuppurative, raised and hemorrhagic,

raised and fibrinosuppurative, depressed ± blood clot, depressed and fibrinosuppurative) (Sykes et al., 2015). The esophageal mucosa was examined during the removal of the endoscope, checking for the presence or absence of ulcers and/or esophagitis.

### *Electrocardiogram*

The electrocardiographic examinations were performed by computerized method with a veterinary electrocardiogram (ECG Acquisition Module for Computer (ECG - PC version Windows 95) Brazilian Electronic Technology (BET), which consists of an electronic circuit externally connected to a notebook with the software installed on the hard disk. The electrocardiogram was performed in the six leads of the frontal plane (I, II, III, aVR, aVL, and aVF), at a speed of 50 mm/s and sensitivity set to 1 cm = 1 mV, over 5 min. The recording was carried out without any kind of sedation, tranquilization or anesthesia. To record the frontal plane derivation, the four electrodes used were alligator clips moistened with alcohol, fixing the positive electrodes, yellow ("left thoracic limb") and red ("right thoracic limb") in the region above the humerus-radius-ulnar joint and the negative electrodes, black ("right pelvic limb") and green ("left pelvic limb") proximal to the femorotibial and patellar joint. The duration of each electrocardiographic recording was five minutes. Interpretations of the electrocardiographic tracings were performed in lead II, and the following parameters were analyzed: P and T wave duration, QRS complex and PR and QT intervals in milliseconds (ms); and HR (b/min). The Student-Newman-Keuls (SNK) statistical



test was performed with a 5% significance level. Statistical analyzes were performed using SAS 9.2 software (SAS Inst., Inc., Cary, NC). The values were compared with the reference values for equine species according to Knottenbelt and Malalana (2015).

## Results and Discussion

The oral paste formulated for the experiment was well accepted by the horses and proved to be palatable. In a study comparing the absorption of meloxicam (oral granular presentation) in animals subjected to food fasting and animals which were fed, it was observed that the drug has good bioavailability by the oral route in both groups, confirming that the drug can be administered at any time of the day without loss of

efficacy however, it may cause differences in pharmacokinetics and in the time to reach maximum serum concentration (Mendoza et al., 2019).

On physical examination, no clinical alterations were observed, and there were no alterations in the level of consciousness, posture, appetite, or coloring of mucous membranes. The other physiological parameters are listed in Table 1. There was a statistically significant difference only in terms of HR when comparing T7 measurement to T0 for the HR variable. The CRT did not show any variability (value = 2 s).

Table 2 details the composition and calculated nutritional values of the diets used during the four egg production cycles.

**Table 1**

**Different letters in the same row indicate that there was a significant difference ( $p < 0.05$ ) in relation to T0, by the Kruskal-Wallis test, adopting a 5% significance level. \* According to the clinical examination proposed by Speirs (1999). Timepoints in days.**

Parameter	T0	T7	T14	T21	T28	Reference values*
HR (beats/min)	52±3.0 <sup>a</sup>	34±2.4 <sup>b</sup>	40±4 <sup>a</sup>	40±1.5 <sup>a</sup>	40±2.01 <sup>a</sup>	30 to 40
RR (breaths/min)	32±2.7 <sup>a</sup>	28±2.2 <sup>a</sup>	20±2.1 <sup>a</sup>	36±3.7 <sup>a</sup>	28±1.74 <sup>a</sup>	18 to 20
Temperature (°C)	37.5±0.1 <sup>a</sup>	37.5±0.1 <sup>a</sup>	37.7±0.1 <sup>a</sup>	37.5±0.1 <sup>a</sup>	37.8±0.1 <sup>a</sup>	38±1
Weight (kg)	415.57±52.18 <sup>a</sup>	402.14±42.40 <sup>a</sup>	409±46.87 <sup>a</sup>	412±47.72 <sup>a</sup>	418.57±51.0 <sup>a</sup>	-

Different letters in the same row indicate that there was a significant difference ( $p < 0.05$ ) in relation to T0, by the Kruskal-Wallis test, adopting a 5% significance level. \* According to the clinical examination proposed by Speirs (1999). Timepoints in days.

Prolonged use of NSAIDs can lead to the development of various pathologies, such as those of the gastrointestinal system, resulting in pain episodes (Van Galen et al., 2021). Pain and inflammation trigger a range of physiological changes, including decreased appetite, decreased water intake, vasoconstriction, increased systemic vascular resistance, increased heart rate and cardiac output, reduced gastrointestinal and urinary tone, increased musculoskeletal tone, hypoventilation, increased blood clotting time, fibrinolysis, and platelet aggregation. However, many of the parameters measured are not exclusively affected by pain but also by a variety of other factors, including hydration status, perfusion, sepsis, fear, anxiety, and sedative or analgesic use (Alves et al., 2016). Therefore, long-term studies on the effects of meloxicam on pathological conditions are necessary.

In clinical practice, when faced with alterations in clinical and laboratory tests, we must consider that values found outside the reference intervals for the species do not, by themselves, indicate the potential for disease; therefore, the interpretation of clinical and epidemiological data (Alves et al., 2016) is necessary. In addition, the values reported in the literature vary considerably, which has generated debates in the veterinary profession (Kerr, 2003).

In a study in which meloxicam was given at a dose of 3 mg/kg (5 times the recommended dose), six (out of seven) animals demonstrated alterations in physical examination, clinical pathology or both. In the case of one of the horses, the colon was impacted at the conclusion of the study, but

the animal showed no signs of abdominal discomfort, suggesting that meloxicam may have masked the effects of the discomfort associated with the accumulation of food intake; it is possible that intestinal motility may have been affected by the pharmacological agent (Noble et al., 2012).

In our study, no changes were observed in the intestinal motility of the animals, and no alterations were observed in the feces. The results of studies in which the effect of coxibs and non-selective NSAIDs on small intestinal motility in horses demonstrated that the non-selective inhibitors did not cause important effects on motility, apart from tonic inhibition demonstrated by flunixin meglumine. Certain COX-2 selective inhibitors (celecoxib, DUP-398 and NS-697) have been reported to reduce tonic contraction and spontaneous phasic contractions, whereas the prostaglandin (PG) receptor antagonists were found to be ineffective, supporting the hypothesis that the effects of COX enzyme inhibitors on horse small intestinal motility are not linked to PG depletion (Menozzi et al., 2009).

The mean values of blood count, total protein, fibrinogen and bleeding time are presented in Table 2. The erythrocyte, hemoglobin, and hematocrit count, as well as MCH and segmented neutrophils showed significant differences ( $p < 0.05$ ) at T14 compared to T0. Although the counts of erythrocytes, hemoglobin and hematocrit were all below the reference values for the species, no clinical alterations were observed in the animals throughout the experimental period.

With respect to albumin, CK, GGT, FA, creatinine, urea and glucose, there were no significant differences ( $P < 0.05$ ) between the values obtained at T0 and the corresponding values at subsequent timepoints. The significant reductions ( $P < 0.05$ ) in AST levels at T7 and T14 compared to the T0 values are within the reference range for equine species (Table 3). The CRP results were always nonreactive, indicating no inflammatory reaction ( $< 6$  mg/L).

In an experimental study using phenylbutazone (non-selective NSAIDs) in healthy horses for a prolonged time period (21 days, dose 8.8 mg/kg, SID), decreases in albumin and plasma protein concentrations and neutrophil counts were reported. The plasma albumin concentrations decreased from days 10 to 21 of treatment, and two (of eight horses) developed right dorsal colitis (McConnico et al., 2008). Some researchers have hypothesized that right dorsal colitis, especially subclinical, can occur without declines in plasma albumin concentration (Van Galen et al., 2021). Such findings are not reported with the use of COX-2 inhibitors in treatments in which the recommended dose (standard dose for up to 14 days) was not exceeded. Similarly, in the present study, there was no evidence of biochemical

alterations, even though meloxicam was used for twice the recommended time.

In research conducted in Australia using the conventional dose of meloxicam in horses for a period of 42 days, the drug was well tolerated by all seven animals in the study, with no accumulation of the drug in plasma, and the animals had no alteration in any of the physiological and physical parameters as determined by physical examination (including weight), hematology, serum biochemistry, urinalysis or bone marrow cytology; however, higher doses (1.8 and 3 mg/kg for 14 days) were associated with decreased total serum protein and albumin concentrations, gastrointestinal damage, renal damage, and bone marrow dyscrasia (Noble et al., 2012).

In horses, the detection of renal injury is difficult due to the absence of efficient early markers and this injury is generally detected belatedly, based on serum concentrations of urea and creatinine. The latter is an indicator used to evaluate the glomerular filtration rate but only increases significantly with a loss of approximately 75% of the glomerular filtration rate, demonstrating severe damage to the nephrons (Savage et al., 2019).



**Table 2**  
**Mean and standard deviation of blood count, total protein, fibrinogen, and bleeding time at the five timepoints (T). Meloxicam was administered at a dose of 0.6 mg/kg, orally, once a day, for 28 days to 7 healthy horses**

Parameter	T0	T7	T14	T21	T28	Reference values*
Erythrocytes ( $\times 10^6/\text{mm}^3$ )	7.34 $\pm$ 0.48 <sup>a</sup>	6.94 $\pm$ 0.56 <sup>a</sup>	6.43 $\pm$ 0.52 <sup>b</sup>	6.71 $\pm$ 0.54 <sup>a</sup>	7.06 $\pm$ 0.34 <sup>a</sup>	6.8 to 12.9
Hemoglobin (g/dL)	7.38 $\pm$ 0.50 <sup>a</sup>	9.97 $\pm$ 0.85 <sup>b</sup>	10.29 $\pm$ 0.86 <sup>b</sup>	10.49 $\pm$ 0.94 <sup>b</sup>	11.29 $\pm$ 0.45 <sup>b</sup>	11 to 19
Hematocrit (%)	33.86 $\pm$ 1.67 <sup>a</sup>	31.29 $\pm$ 3.09 <sup>a</sup>	29.86 $\pm$ 1.12 <sup>b</sup>	31.43 $\pm$ 1.90 <sup>a</sup>	31.43 $\pm$ 1.13 <sup>a</sup>	32 to 53
MCV ( $\mu^3$ )	44.88 $\pm$ 2.06 <sup>a</sup>	44.03 $\pm$ 0.84 <sup>a</sup>	46.33 $\pm$ 2.61 <sup>a</sup>	47.16 $\pm$ 2.79 <sup>a</sup>	45.41 $\pm$ 2.22 <sup>a</sup>	37 to 58
MCH	14.88 $\pm$ 0.61 <sup>a</sup>	14.80 $\pm$ 0.48 <sup>a</sup>	15.82 $\pm$ 0.88 <sup>a</sup>	15.74 $\pm$ 1.01 <sup>a</sup>	16.32 $\pm$ 0.62 <sup>b</sup>	13 to 18
MCHC (g/dL)	33.02 $\pm$ 0.38 <sup>a</sup>	34.52 $\pm$ 3.89 <sup>a</sup>	34.55 $\pm$ 1.63 <sup>a</sup>	33.30 $\pm$ 0.95 <sup>a</sup>	36.06 $\pm$ 2.30 <sup>a</sup>	31 to 37
Leukocytes ( $\times 10^3/\text{mm}^3$ )	10.73 $\pm$ 1.54 <sup>a</sup>	10.04 $\pm$ 1.58 <sup>a</sup>	9.55 $\pm$ 1.46 <sup>a</sup>	10.36 $\pm$ 1.33 <sup>a</sup>	9.78 $\pm$ 1.31 <sup>a</sup>	5.4 to 14.3
Segmented neutrophils (%)	51.86 $\pm$ 4.67 <sup>a</sup>	46.86 $\pm$ 7.69 <sup>a</sup>	34.14 $\pm$ 11.67 <sup>b</sup>	53.00 $\pm$ 5.91 <sup>a</sup>	49.86 $\pm$ 4.91 <sup>a</sup>	22 to 72
Lymphocytes (%)	42.57 $\pm$ 6.26 <sup>a</sup>	46.86 $\pm$ 9.24 <sup>a</sup>	46.71 $\pm$ 12.13 <sup>a</sup>	41.00 $\pm$ 5.44 <sup>a</sup>	36.57 $\pm$ 4.72 <sup>a</sup>	17 to 68
Eosinophils (%)	3.71 $\pm$ 1.60 <sup>a</sup>	3.43 $\pm$ 2.57 <sup>a</sup>	10.29 $\pm$ 8.6 <sup>a</sup>	2.85 $\pm$ 2.19 <sup>a</sup>	7.14 $\pm$ 4.29 <sup>a</sup>	0 to 10
Monocytes (%)	2.28 $\pm$ 1.38 <sup>a</sup>	2.28 $\pm$ 1.25 <sup>a</sup>	5.00 $\pm$ 1.52 <sup>a</sup>	2.57 $\pm$ 1.39 <sup>a</sup>	4.00 $\pm$ 2.70 <sup>a</sup>	0 to 7
Platelets ( $\times 10^3 \mu\text{L}$ )	228.0 $\pm$ 24.36 <sup>a</sup>	233.7 $\pm$ 34.54 <sup>a</sup>	195.4 $\pm$ 86.37 <sup>a</sup>	240.9 $\pm$ 27.30 <sup>a</sup>	242.1 $\pm$ 28.88 <sup>a</sup>	100 to 350
Fibrinogen (mg/dL)	257.1 $\pm$ 97.5 <sup>a</sup>	314.2 $\pm$ 106.9 <sup>a</sup>	314.2 $\pm$ 106.9 <sup>a</sup>	314.2 $\pm$ 106.9 <sup>a</sup>	257.1 $\pm$ 97.5 <sup>a</sup>	150 to 400
Total Protein (g/dL)	6.88 $\pm$ 0.25 <sup>a</sup>	6.88 $\pm$ 0.25 <sup>a</sup>	7.25 $\pm$ 0.32 <sup>a</sup>	6.82 $\pm$ 0.33 <sup>a</sup>	6.88 $\pm$ 0.25 <sup>a</sup>	5.2 to 7.9
Bleeding time (sec)	70.57 $\pm$ 10.16 <sup>a</sup>	102.42 $\pm$ 36.65 <sup>a</sup>	174.71 $\pm$ 60.58 <sup>a</sup>	123.71 $\pm$ 45.49 <sup>a</sup>	116.14 $\pm$ 25.46 <sup>a</sup>	120 to 180

Data represent the mean  $\pm$  standard deviation. Data followed by equal letters do not differ from ANOVA, followed by the Bonferroni post hoc test at 5% probability in relation to T0. \*Values according to Kaneko et al. (2008). Timepoints in days.

**Table 3**  
**Mean and standard deviation of serum biochemistry at the five timepoints (T). Meloxicam was administered at a dose of 0.6 mg/kg, orally, once a day, for 28 days to 7 healthy horses**

Parameter	T0	T7	T14	T21	T28	Reference values*
Glucose (mg/dL)	68.43±8.86 <sup>a</sup>	71.43±8.65 <sup>a</sup>	61.00±11.90 <sup>a</sup>	61.86±10.65 <sup>a</sup>	77.57±6.70 <sup>a</sup>	75 to 115
AST (U/L)	229.0±19.18 <sup>a</sup>	220.1±16.18 <sup>b</sup>	189.4±15.37 <sup>b</sup>	194.4±12.45 <sup>a</sup>	213.0±27.40 <sup>a</sup>	0 to 366
CK (U/L)	282.9±74.45 <sup>a</sup>	318.9±70.40 <sup>a</sup>	306.6±113.5 <sup>a</sup>	318.9±95.18 <sup>a</sup>	214.1±43.29 <sup>a</sup>	0 to 140
GGT (U/L)	26.14±12.67 <sup>a</sup>	21.71±3.40 <sup>a</sup>	21.00±3.10 <sup>a</sup>	20.29±3.30 <sup>a</sup>	20.43±3.10 <sup>a</sup>	0 to 62
Albumin (g/dL)	2.63±0.16 <sup>a</sup>	2.28±0.38 <sup>a</sup>	2.57±0.18 <sup>a</sup>	2.40±0.10 <sup>a</sup>	2.36±0.32 <sup>a</sup>	2.6 to 3.7
Urea (mg/dL)	40.86±4.91 <sup>a</sup>	43.14±6.23 <sup>a</sup>	35.29±3.94 <sup>a</sup>	44.14±5.39 <sup>a</sup>	35.29±5.15 <sup>a</sup>	21 to 51
FA(U/L)	239.3±54.91 <sup>a</sup>	273.9±62.11 <sup>a</sup>	249.0±56.90 <sup>a</sup>	278.1±66.33 <sup>a</sup>	292.0±67.51 <sup>a</sup>	0 to 395
Creatinine (mg/dL)	0.79±0.12 <sup>a</sup>	0.97±0.1 <sup>a</sup>	0.93±0.07 <sup>a</sup>	0.93±0.10 <sup>a</sup>	0.94±0.24 <sup>a</sup>	1.2 to 1.9

Values with the same letters do not differ from ANOVA followed by Bonferroni post hoc test at 5% probability in relation to T0. \*Values according to Kaneko et al. (2008). Timepoints in days.

Urea and creatinine concentrations did not indicate possible renal damage in our study. These indicators were chosen because they are easy to measure under clinical conditions and because there is a possibility that the prolonged use of NSAIDs may induce changes in serum biochemical variables associated with renal function, especially with use over a longer period of time. New serum biomarkers to assess renal function have been investigated in horses, among them cystatin C (CysC) and symmetric dimethylarginine (SDMA). The measurement of CysC has been evaluated in dogs and cats, but attempts to quantify it in equine plasma with human-based immunoassays have been unsuccessful (Schott II & Esser, 2020).

The use of a selective inhibitory NSAID with a non-selective one is also inadvisable. The combination of phenylbutazone with firocoxib (both at standard doses) has been tested in healthy horses: changes in serum

creatinine and total protein concentrations were evident, indicating that the association of these drugs may cause renal disease (Kivett et al., 2014). An important point about coxibs is that their selectivity is only achieved when administered in the correct dosage—overdoses can lead to the same adverse effects as those caused by traditional inhibitors (D. A. Santos et al., 2020).

Each diagnostic method has its pros and cons and situations that enable or hinder its application, leaving the most appropriate choice for each case at the discretion of the veterinarian (Alves et al., 2016). In addition, some factors, such as inflammatory alterations related to a primary disease, fluid administration, primary disease and/or related complications, may interfere with the detection of changes in blood parameters, making these parameters less useful in clinical settings (Van Galen et al., 2021).

In the present study, the results of the bleeding time test did not reveal any abnormalities of hemostasis. The bleeding test is considered the most reliable *in vivo* test to evaluate primary hemostasis: interactions between the vascular endothelium and platelets result in the formation of the primary hemostatic plug, which provides temporary sealing to the site of vascular injury (Kerr, 2003; Luna et al., 2007).

NSAIDs can prevent or reduce the formation of thromboxane A2 in platelets, impairing platelet adhesion. In a study in which anti-inflammatory drugs were administered to dogs for 90 days, carprofen was the only drug to significantly increase bleeding time compared to baseline values, even though it did not alter the hemostatic variables (Luna et al., 2007). The authors of the study concluded that all of the NSAIDs studied induced only minor clinically unimportant changes in hemostatic variables and serum biochemistry in dogs; carprofen also accounted for the lowest frequency of gastrointestinal adverse effects, followed by meloxicam, etodolac, flunixin and ketoprofen.

In the present study of meloxicam in horses, at no time did the animals show signs of abdominal discomfort, nor were changes observed in the esophagus. At T14, five animals were classified as G1, presenting discrete hyperkeratosis and hyperemia in the background aglandular region. At T21, all seven animals presented with hyperkeratosis and hyperemia; moreover, in the animals that had already had alterations at T14, a slight worsening of the lesions was observed (remaining in G1), as well as some effects in the *margo plicatus* region. At T28 there was regression of signs in four animals (remaining in G1), with the observation of

discrete hyperkeratosis associated with hypersecretion of mucus in two animals, hyperkeratosis in one and slight hyperemia in the other. In the other three animals, no changes were observed, and they were returned to the G0 classification.

In equines, several factors influence the development of ESGD and all share the characteristic of increasing exposure of the squamous mucosa to acid. *In vitro* experiments have shown that squamous mucosa cells are susceptible to hydrochloric acid (HCl) and volatile fatty acid (VFA) in a pH-, dose-, and time-dependent manner (Andrews et al., 2006). The damage to the outer cell barrier is induced by HCl followed by diffusion into the squamous cells of the stratum spinosum, which can result in ulceration (Nadeau et al., 2003). The by-products of bacterial sugar fermentation in concentrated diets—not only VFA and lactic acid but also bile acids—have been shown to act synergistically with HCl (Nadeau et al., 2003). The relationship between exposure of the squamous mucosa to acidic content and training is well described. Excessive exposure of the squamous mucosa results from acidic gastric contents being pushed upward by increased intra-abdominal pressure, as occurs at paces faster than walking (Lorenzo-Figueras & Merritt, 2002).

In contrast, the pathophysiology of EGGD is poorly understood. The glandular mucosa differs from the squamous mucosa, which under normal conditions is exposed to highly acidic gastric contents with a relatively stable pH in the ventral portion of the stomach, ranging between 1 and 3 (Merritt et al., 2003). Whereas ESGD results from exposure of the mucosa unaccustomed to acidity, EGGD is believed to result from a breakdown of the

normal defense mechanisms that protect the mucosa from acidic gastric contents. The factors that contribute to the breakdown of the protective layer have not yet been elucidated in horses; however, in humans, *Helicobacter pylori* and NSAIDs are known to be the predominant causes of gastric ulceration (Malfertheiner et al., 2009), and this has motivated research on these same mechanisms in horses.

In a study conducted in Brazil to evaluate the efficacy and safety of meloxicam in horses, the animals were submitted to the dosage recommended in the literature, for a period of 14 days, SID, resulting in no alteration in vital parameters, in the bleeding time test, nor in the hematological and biochemical profiles, but slight alterations on the gastric mucosa were reported (Veronezi et al., 2006). These findings are similar to the results we report here: even though meloxicam was given for twice as long a period, which allows us to affirm that the use of meloxicam under the conditions described in this study did not cause relevant gastric lesions.

The mechanism of NSAID-induced gastric disease in horses has not yet been determined. Although anti-inflammatory-associated ulceration is often attributed to a decrease in basal gastric prostaglandins, this has not yet been fully elucidated (Pedersen et al., 2018). In a study in which gastric glandular disease was induced in horses via phenylbutazone at a dose of 4.4 mg/kg, BID, for 7 days, all animals developed the condition with Grade  $\geq 2$ , but the drug did not promote a decrease in basal gastric glandular PGE2 levels (Pedersen et al., 2018).

The greater or lesser likelihood of an NSAID causing adverse effects is contingent on its ability to selectively inhibit COX-2 alone or inhibit COX-1 jointly. Meloxicam is a preferential inhibitor of COX-2, with a much lower selectivity ratio than the selective inhibitor firocoxib (4 and 200, respectively), which also inhibits COX-1 to some extent (Ziegler et al., 2017). These findings have led to the hypothesis that prolonged use of meloxicam may lead to adverse effects common to conventional NSAIDs, especially if used for long periods.

Treatment with acid suppressants is indicated for the management of EGUS. Proton pump inhibitors and H2 antagonists are the most commonly used classes of drugs in veterinary treatment of horses. Omeprazole is superior to ranitidine in the treatment of natural diseases and is the drug of choice for the treatment of EGUS (Sykes et al., 2015). The use of gastric protectors is recommended when administering anti-inflammatory medications to prevent or even treat injuries (Veronezi et al., 2006), and sucralfate is the best studied of these (Sykes et al., 2015).

Although gastroscopy is still the gold standard test for diagnosis of EGUS, it is not suitable as a screening method because it is expensive, time-consuming, and not readily available to most veterinarians (Hewetson et al., 2017). Other more effective, less invasive, and cheaper diagnostic techniques have been evaluated, such as serum proteins as biomarkers for EGUS (Tesena et al., 2019) and the sucrose permeability test (Hewetson et al., 2017), but more research is needed.

Laboratory tests should not be ruled out in the investigation of EGUS, with the additional consideration that although the results of such tests do not change simply due to gastric disorders, important factors (such as anemia and hypoproteinaemia) may predict more serious conditions, including severe ulceration of the pylorus with fibrosis and reduction of the passage of gastric contents (R. S. T. Santos et al., 2018).

Additional effects on the health of the gastrointestinal tract may occur in other ways; for example, stress during hospitalization, sudden changes in food management, changes in appetite, adverse effects of other therapies, and nosocomial illness (Van Galen et al., 2021). Such risks were minimized in our research, as the animals were already adapted

to the environment and the stress caused by confinement in stables was minimal, as they were only stabled the day before diagnostic procedures were carried out. In addition, all the animals had undergone examination at the beginning of the experiment to confirm the absence of previous gastric injury.

All electrocardiographic variables assessed remained within the values considered physiological for equine species (Knottenbelt & Malalana, 2015) (Table 4). This result confirms that meloxicam does not cause interference with electrical impulse conduction in cardiac muscles. Statistical differences were found only at T14, with respect to the variable "P wave duration", but the values remained within the range of what is considered normal.

**Table 4**  
**Mean and standard deviation of electrocardiogram results of the animals in the treated group at the three timepoints (T). Meloxicam was administered at a dose of 0.6 mg/kg, orally, once a day, for 28 days to 7 healthy horses**

Parameter	T0	T14	T28	Reference values*
HR (beats/min)	35 ± 12.8 <sup>a</sup>	38.57 ± 3.15 <sup>a</sup>	39.71 ± 4.23 <sup>a</sup>	30 to 40
P wave duration (ms)	99.86 ± 16.75 <sup>a</sup>	130 ± 13.14 <sup>b</sup>	99.57 ± 18.45 <sup>a</sup>	80 to 200
QRS duration (ms)	118.43 ± 8.63 <sup>a</sup>	121 ± 14.76 <sup>a</sup>	113 ± 18.62 <sup>a</sup>	80 to 170
P-R interval (ms)	262.14 ± 24.46 <sup>a</sup>	277 ± 25.25 <sup>a</sup>	268 ± 26.54 <sup>a</sup>	220 to 560
Q-T interval (ms)	530 ± 33.30 <sup>a</sup>	507.57 ± 34.80 <sup>a</sup>	500.57 ± 28.3 <sup>a</sup>	320 to 640

Different letters in the same row indicate a significant difference ( $p < 0.05$ ) in the Student-Newman-Keuls (SNK) test. ms: milliseconds. \*Values according to Knottenbelt and Malalana (2015). Timepoints in days.



The determination of arrhythmias and conduction disorders is still the main indication for ECG in horses. The electrocardiographic examination is an accessible, non-invasive, and easy-to-perform method in any circumstance, even in field conditions, which helps in the diagnosis and evaluation of heart diseases or even in cardiac dysfunctions secondary to systemic disorders and should always be interpreted in conjunction with a clinical examination of the cardiovascular system (Fernandes et al., 2004). It is known that, in humans, all NSAIDs can be associated, although to varying extents, with increased risk of cardiovascular adverse events and may increase arterial pressure (Mendes et al., 2012), especially when used at high doses and for prolonged periods (Shi & Klotz, 2008).

The hypothesis that COX-2 inhibitors would present beneficial effects without the gastrointestinal and renal toxicity associated with conventional inhibitors has directed the search for new drugs selective for this isoenzyme; however, in humans, the exclusive COX-2 inhibition has been associated with serious cardiovascular by causing an imbalance between anti- and pro-thrombotic factors, with a predominance of thromboxanes (TXA<sub>2</sub>) to the detriment of prostacyclins (PGI<sub>2</sub>). These deleterious effects have prompted the removal of some drugs of this category from the market (Mendes et al., 2012). Despite the early success of coxibs, it soon became apparent that the selective inhibition for COX-2 was much more complex than suggested by the initial hypothesis. Controlled clinical trials have shown that coxibs increase the risk of cardiovascular complications affecting approximately 1 to 2% of human patients.

It is estimated that the drugs rofecoxib and celocoxib caused more than 26,000 deaths in the first five years of their release in the United States (Vaithianathan et al., 2009).

In horses, there is not the same tendency of cardiovascular alterations as seen with the use of COX-2 inhibitors in humans, which suggests that it may be safe for use in treating horses (Ziegler et al., 2017). Our study was the first to evaluate meloxicam in terms of electrocardiography indicators; no alterations were evident in the electrocardiograms, indicating no adverse effects, however further studies involving a larger number of animals tested and more cardiac evaluation tests are needed.

## Conclusions

The administration of meloxicam (0.6 mg/kg, orally, once a day) to healthy horses for 28 consecutive days resulted in slight changes but no adverse effects, as indicated by the results of the bleeding time test and assessment of various clinical, hematological, biochemical, gastroscopic, and electrocardiographic parameters. The results of our study suggest that meloxicam (at the present dosage regimen) is safe to use in veterinary treatment of horses.

## Acknowledgments

The authors thank the Research and Extension Group in Equidae (GRUPEQUI), Federal University of Alagoas, the Federal University of Western Bahia for financial support, and the Editage ([www.editage.com.br](http://www.editage.com.br)) for English language editing.

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