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Original Article - Veterinary Medicine

Effects of trometamol ketorolac eye drops on blood count, serum biochemistry, and urinalysis in healthy dogs

[*Efeitos do colírio de cetorolaco de trometamol sobre o hemograma, a bioquímica sérica e a urinálise em cães saudáveis*]

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ABSTRACT

This study aimed to evaluate whether the use of trometamol ketorolac for 30 consecutive days may change the blood count, the serum biochemistry profile, and the urinalysis of healthy dogs. Eleven small breed dogs (4.6-10kg), with ages ranging from 1 to 9 years were enrolled in the study. Dogs received 40µL of 0.4% trometamol ketorolac eye drops, every 12 h in both eyes for 30 consecutive days. Blood and urine samples were collected at baseline, and following 15 and 30 days of the beginning of the treatment. Creatinine levels increased significantly at day 15 (1.21±0.1mg/dL) and 30 (1.22±0.1mg/dL) when compared with baseline (0.94±0.1mg/dL) (P<0.01). Significantly increased values of serum potassium were observed only at day 30 (4.66±0.15mEq/L), when compared with day 15 (4.32±0.12mEq/L) and baseline (4.36±0.15mEq/L) (P<0.05). The other hematological and biochemical parameters did not change significantly during the study (P>0.05). From observations of our study, it can be concluded that the instillation of trometamol ketorolac for 30 consecutive days did not cause clinically relevant changes in the blood count, biochemistry profile and in the urinalysis of healthy dogs.

Keywords: creatinine, sodium, lactate, topical NSAID, systemic absorption

RESUMO

Objetivou-se avaliar se a instilação de cetorolaco de trometamol, durante 30 dias contínuos, alteraria o hemograma, a bioquímica sérica e a urinálise em cães saudáveis. Dez cães de pequeno porte (4,610 kg), com idades entre um e nove anos, foram recrutados para a pesquisa. Os cães foram tratados a cada 12h, com 40µL de cetorolaco de trometamol a 0,4% em ambos os olhos, durante 30 dias consecutivos. Coleta de sangue foi realizada para obtenção de valores basais e aos 15 e 30 dias após o início do tratamento. A creatinina se elevou de forma significativa decorridos 15 (1,21±0,1mg/dL) e 30 dias (1,22±0,1 mg/dL) da avaliação basal (0,94±0,1mg/dL) (P<0,01). O potássio se elevou significativamente apenas ao 30º dia (4,66 ± 0,15mEq/L), comparativamente à avaliação do 15º dia (4,32±0,12mEq/L) e à basal (4,36±0,15mEq/L) (P<0,05). Os demais parâmetros hematológicos e bioquímicos não se alteraram de forma significativa durante o estudo (P>0,05). Conclui-se que a instilação de cetorolaco de trometamol por 30 dias não provocou alterações relevantes no hemograma, no perfil bioquímico e na urinálise de cães saudáveis.

Palavras-chave: creatinina, sódio, AINE tópico, absorção sistêmica

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclo-oxygenase enzyme in the arachidonic acid pathway, which consequently decreases the production of pro-inflammatory mediators (Gilmour, 2004). Trometamol ketorolac (TK) is an NSAID that is commonly prescribed as an ophthalmic solution in veterinary ophthalmology. In comparison to topical corticosteroids, topical NSAIDs are a

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more prudent therapeutic choice when treating patients with uveitis arising from infectious ocular diseases and those with diabetes who present with ulcerative keratouveitis or stromal abscesses (Gilmour, 2004).

In dogs, the reported side effects associated with the use of systemic NSAIDs include gastrointestinal disturbances, blood dyscrasias, hypoproteinemia, bronchoconstriction, hepatotoxicity, and nephrotoxicity (Gilmour, 2004; Lieser *et al*., 2021). Following topical application of ophthalmic solutions, a portion of the drug is absorbed systemically via conjunctival vessels and nasolacrimal drainage, where it can be absorbed by the nasal mucosa or swallowed (Segabb *et al.*, 2020; Ewald *et al.*, 2022). Occurrence of adverse systemic events secondary to topical administration of NSAIDs, although rare, has been reported in human beings as an *in vitro* inhibition of platelet function and exacerbation of bronchial asthma (Falcinelli *et al.*, 2019; Syed *et al*., 2021). Systemic absorption following the instillation of ophthalmic NSAIDs has been confirmed in chickens, rabbits, and cats (Hsu *et al.*, 2015; Lanuza *et al.*, 2016; Griggs *et al.*, 2017; Pereira *et al.*, 2019). In chickens, topical administration of diclofenac to one or both eyes decreased total protein levels, but it did not alter plasma uric acid levels (Griggs *et al*., 2017). Similarly, Pereira *et al.* demonstrated that rabbits treated for 90 days with a topical TK ophthalmic solution did not develop adverse systemic events based on clinical signs, food consumption, laboratory findings, and histopathology of the kidneys and liver. Two studies on healthy cats showed that the instillation of diclofenac or flurbiprofen as ophthalmic solutions did not induce clinically relevant abnormalities in the total blood count, urinalysis, or serum biochemistry profile (Hsu *et al.*, 2015; Lanuza *et al.*, 2016). However, in one of these studies, Hsu *et al.* reported that diclofenac-treated cats had a significantly lower glomerular filtration rate (GFR), presumably associated with iatrogenic hypovolemia. No previous reports or studies have evaluated the possible adverse systemic events following the administration of topical NSAIDs as ophthalmic solutions in dogs. Considering that dogs are commonly treated with topical medications, including NSAIDs, for long periods before and after cataract surgery, it is important to evaluate the possible changes in blood parameters in individuals receiving this class of drugs. Therefore, the current study aimed to investigate whether the instillation of TK for 30 consecutive days would affect the values of hematocrit, hemoglobin, platelets, leukogram, albumin, alanine aminotransferase (ALT), alkaline phosphatase (AP), urea, creatinine, lactate, sodium, potassium, and urinalysis parameters in healthy dogs.

MATERIALS AND METHODS

This study was approved by the institutional Committee for Ethics in the Use of Animals of [MASKED FOR REVIEW] (protocol # 23108.043452/2022-05). Four castrated male dogs and seven spayed bitches (n=11) aged 2–7 years and weighing 4.6–10.3 kg were included in this study. The breeds included were as follows: Schnauzer (1), Pincher (3), Dachshund (1), Yorkshire Terrier (2), and mixed breed (4). The exclusion criteria were current or recent (20 days before) treatment with any systemic or topical ophthalmic medications and current or history of ophthalmic or any other known systemic comorbidities.

General physical and ophthalmic examinations were performed on each dog prior to its inclusion in the study. Further, 5 mL of blood was collected from the jugular vein for hematological evaluation (hematocrit, hemoglobin, platelets, leukogram, and total protein) and serum biochemical analysis (albumin, ALT, AP, urea, creatinine, lactate, sodium, and potassium). An automated hematological (pocH-100iv Diff, Sysmex, Brazil) and biochemical analyzers (CM 250, Wiener lab group, Brazil) were used to perform some of the laboratorial exams described above. Hematocrit and platelet counts were determined manually using light microscopy. Lactate levels were determined with a portable lactimeter (Accutrend Plus®, Roche, Brazil). Sodium and potassium levels were measured using an electrolyte analyzer. (EasyLite, Grupo Kovalent, Brazil).

Fresh urine samples were collected by ultrasound-guided cystocentesis in female dogs and urethral catheterization in male dogs for urinalysis and determination of the urine protein-to-creatinine (UPC) concentration ratio. In the urinalysis, urine specific gravity was measured using refractometry (Atago Refractometer®).

Urine pH and other chemical parameters were evaluated using reagent test strips (Combur10 Test UX, Roche, Brazil) and recorded on a specific reader (Urisys 1100, Roche, Brazil). All laboratory procedures were performed on each dog approximately one week before the start of the study to ensure that all individuals were healthy and to collect baseline values.

Once selected, the dogs were administered 40µL of 0.4% TK ophthalmic solution (Acular® LS, Allergan, Guarulhos, SP, Brazil) in both eyes every 12 h for 30 consecutive days. The general condition of the animals and gastrointestinal tolerance (food intake, vomiting, diarrhea, and melena) to NSAIDs were assessed daily. The general condition of the animals and their gastrointestinal tolerance (food intake, vomiting, diarrhea, and melena) to NSAIDs were assessed daily. Physical examination, body weight, and blood and urinary parameters were assessed one day before, as well as 15 and 30 days after starting treatment with TK. All dogs included in the study were kept in their homes and were treated and examined daily by veterinarians enrolled in the study. For blood and urine sample collection, the dogs were brought to the hospital and managed by the same veterinarians.

The sample size was determined with a 5% alpha error rate and 80% power based on standard deviations and equivalence limit values for hematological and biochemical parameters detected in previously published studies that used six dogs/group as an animal model for NSAID tolerance (Luna *et al*., 2007; Fusellier *et al.*, 2008; Borges *et al.*, 2013). Greater than or equal to 7 dogs was calculated as the appropriate sample size (www.sealedenvelope.com). The Shapiro–Wilk test was used to assess data normality. All variables were compared using a one-way analysis of variance for repeated measures, followed by Bonferroni´s multiple comparison test to assess the possible differences in values observed on days 15 and 30 compared to the baseline values. Differences were considered statistically significant at $P<0.05$ (Prism 4.0-GraphPad Software inc, California, USA). The data are expressed as mean ± standard deviation.

RESULTS AND DISCUSSION

To our knowledge, this is the first study to evaluate the possible adverse events in dogs treated with the TK ophthalmic solution for 30 consecutive days. Although systemic absorption of TK was not examined in the present study, it might have occurred because prednisolone and dexamethasone were detected in the plasma of healthy dogs 1, 7, and 14 days after both drugs were administered as ophthalmic solutions (Segabb *et al.*, 2020; Ewald *et al.*, 2022). Additionally, systemic absorption following the instillation of ophthalmic NSAIDs has been confirmed in chickens (diclofenac), rabbits (diclofenac and TK), and cats (flurbiprofen and diclofenac) (Griggs *et al.*, 2017; Pereira *et al.*, 2019; Hsu *et al.*, 2015; Lanuza *et al.*, 2016). In the present study, the dogs were not kept in a controlled environment. In the present study, the dogs were not kept in a controlled environment. However, they were all owned by veterinarians enrolled in the study. All participants lived in the same city [MASKED FOR REVIEW] and were treated during the same period (from July to august of 2022), which made treatments and examinations possible daily.

In the present study, instillation of TK for 30 consecutive days did not result in abnormalities in red blood cells. Similarly, a previous study conducted on dogs showed that oral administration of meloxicam and carprofen for 10 or more days did not result in erythrocyte dyscrasia or oxidative erythrocyte damage ($P>0.05$) (Table 1). Similarly, a previous study conducted on dogs showed that oral administration of meloxicam and carprofen for 10 or more days did not result in erythrocyte dyscrasia or oxidative erythrocyte damage (Lieser *et al*., 2021). Coagulation disorders, such as inhibition of platelet cyclo-oxygenase, reduced formation of pro-aggregatory eicosanoid thromboxane A_2, and prevention of platelet aggregation, are adverse effects that may occur after long-term systemic administration of NSAIDs (Gilmour, 2004). The platelet count, prothrombin time, and thromboplastin time did not change significantly in rabbits receiving TK or diclofenac as ophthalmic solutions for 90 consecutive days (Pereira *et al.*, 2019). Nevertheless, no previous studies or reports have evaluated the possible adverse events related to the blood or platelet count of dogs that received

NSAIDs as ophthalmic solutions. The results of the present study showed that instillation of TK as an ophthalmic solution did not change the parameters (P>0.05) after 15 and 30 days of treatment (Table 1). An *in vitro* study conducted using blood from humans treated with ophthalmic NSAIDs showed that indomethacin, but not diclofenac, had a significant systemic antiplatelet effect (Falcinelli *et al.*, 2019). However, such an evaluation has not been performed in veterinary medicine. One limitation of the present study is the lack of assessment of clotting time, which is one of the best *in vivo* tests for evaluating primary hemostasis (Luna *et al.*, 2007). A previous study on dogs showed that systemic administration of different NSAIDs for 90 consecutive days did not change the platelet count, but it significantly increased the clotting times (Luna *et al.*, 2007).

Table 1. Mean ± standard deviation values f of hematocrit (Htc), hemoglobin (Hgb), platelets, total leukocytes (Leuko), albumin, alanine aminotransferase (ALT), alkaline phosphatase (AP), urea, creatinine, lactate, sodium (Na), potassium (K) during baseline, and after the instillation of trometamol ketorolac for 15 and 30 days in healthy dogs

	Reference	Baseline	Day 15	Day 30	P value
Hgb (g/dl)	12 - 18	16.05 ± 2.00	16.64 ± 1.63	16.34 ± 1.75	0.44
Htc (%)	37 - 55	47.65 ± 5.68	50.41 ± 5.52	49.82 ± 4.87	0.13
Leuko (cells x 10^3 /µl)	6 - 17	9.54 ± 2.69	9.51 ± 2.46	8.84 ± 2.50	0.36
Platelets (cells x10^3/µl)	175 - 500	344.7 ± 123.1	335.5 ± 80.43	291.4 ± 108.2	0.09
Total protein (g/dL)	5.5 – 8.0	6.81 ± 0.53	7.16 ± 0.91	7.23 ± 0.79	0.06
Albumin (g/dl)	3.2 – 4.1	3.19 ± 0.21	3.61 ± 0.24 [a]	3.43 ± 0.24	**<0.001**
ALT (U/L)	21 – 102	51.91 ± 43.83	55.45 ± 33.73	46.27 ± 20.11	0.58
AP (U/L)	20 – 156	70.27 ± 19.19	74.27 ± 20.69	71.55 ± 23.10	0.58
Urea (mg/dL)	21 - 59.9	33.55 ± 8.23	40.82 ± 12.25	38.91 ± 10.83	0.20
Creatinine (mg/dL)	0.5 - 1.5	0.95 ± 0.17	1.17 ± 0.21**[a]**	1.13 ± 0.21	**0.0006**
Lactate (mmol/L)	2.0 - 3.9	2.67 ± 0.51	3.25 ± 0.48	3.25 ± 1.15	0.37
Na (mmol/L)	141 – 154	141.3 ± 3.21	143.9 ± 3.27 **[a]**	145.2 ± 1.42[b]	**<0.01**
K (mmol/L)	3.90 - 5.65	4.37 ± 0.13	4.40 ± 0.15	4.56 ± 0.19	0.06

a,b: Differed significantly from baseline. c: Differed significantly from baseline. c,d: Differed significantly between each other. *

Hepatocellular toxicosis associated with alternate administration of oral carprofen and meloxicam has been reported in Siberian Husky (Nakagawa *et al*., 2005). However, in a study on cats treated with topical ophthalmic diclofenac four times/day for seven consecutive days, no changes were detected in the serum ALT, AP, or γ-glutamyl transpeptidase levels (Hsu *et al.*, 2015). Similarly, the histology of the liver was normal in rabbits treated with topical TK or diclofenac ophthalmic solution for 90 days (Pereira *et al.*, 2019). Normal ALT and AP values have also been reported in dogs that received oral NSAIDs for 90 consecutive days (Luna *et al.*, 2007). In the present study, ALT and AP levels remained within the reference range for dogs and did not change significantly throughout the study period (P=0.58) (Table 1). Despite this finding, one or two traces of bilirubin were found in the urinalysis of 6/11 dogs throughout the experiment. However, none of these dogs showed abnormal ALT or AP levels during the evaluations carried out on days 15 and 30, and the mean values of urinary bilirubin did not change significantly throughout the study (P=0.18) (Table 2). Serum bilirubin levels were not measured in this study. However, bilirubin assessed using a urine dipstick represents conjugated bilirubin, and bilirubinuria often precedes hyperbilirubinemia in most species (Pieche and Wycislo, 2019). One possible explanation for our findings is that trace or a small amount of bilirubinuria may occur in healthy dogs with adequately concentrated urine owing to their low kidney threshold for bilirubin and the ability of their renal tubular epithelial cells to convert heme to unconjugated bilirubin, which is then excreted in the urine (Pieche and Wycislo, 2019). Based on the aforementioned information and other parameters assessed in the urinalysis (Table 2), it is reasonable to assume that the traces of bilirubin found in the urine of these dogs were not associated with the ophthalmic administration of TK.

Table 2. Mean ± standard deviation values of the urinalysis during baseline, and after the instillation of trometamol ketorolac for 15 and 30 days in healthy dogs

	Reference	Baseline	Day 15	Day 30	P value
Leukocytes	Absent	0.00	0.00	0.00	-
Specific gravity	1.015 - 1.045	1.032 ± 11.15	1.038 ± 13.52	1.038 ± 13.34	0.36
Protein	Absent	0.18 ± 0.40	0.09 ± 0.30	0.09 ± 0.30	0.79
Glucose	Absent	0.00	0.00	0.00	-
Ketonic bodies	Absent	0.00	0.00	0.00	-
Bilirubin	Absent	0.09 ± 0.30	0.63 ± 0.80	0.36 ± 0.80	0.18
pH	5.0 - 7.0	6.81 ± 1.07	7.40 ± 0.97	7.00 ± 1.26	0.47
Erythrocytes	0 – 3	0.63 ± 0.92	0.54 ± 0.68	0.36 ± 0.50	0.64
UPC (mg/dL)	< 0.20 – 0.5	0.12 ± 0.14	0.08 ± 0.04	0.06 ± 0.06	0.38

Although urea and creatinine remained within the reference range for dogs throughout the study, the creatinine levels (P=0.0006) increased significantly on day 15 (Table1). Similarly, the ophthalmic solutions diclofenac and flurbiprofen significantly increased (within the reference range) urea and creatinine values in healthy cats without inducing clinically relevant changes (Lanuza *et al.*, 2016). In rabbits, the same enzymes and the histology of the kidneys were normal after 90 days of treatment with topical diclofenac or TK ophthalmic solution (Pereira *et al.*, 2019). Even in dogs that received different NSAIDs for 7, 10, or 90 consecutive days, serum urea and creatinine levels remained within the reference range (Luna *et al.*, 2007; Borges *et al.*, 2013; Fusellier *et al.*, 2008).

Although urea and creatinine concentrations may be used to evaluate renal function, these markers are not sensitive enough to establish an early diagnosis of renal failure because their levels increase only when renal damage is severe (Luna *et al.*, 2007; Borges *et al.*, 2013; Sant'Anna *et al.*, 2019). In contrast, proteinuria may indicate renal damage before the development of azotemia in dogs with kidney disease (Pieche and Wycislo, 2019; Sant'Anna *et al.*, 2019). Normal urine contains little to no detectable protein owing to effective reabsorption by proximal renal tubular epithelial cells (Pieche and Wycislo, 2019). One trace of protein was detected in three different dogs (all females): one at baseline, one on day 15, and one on day 30. This single trace may be associated with postrenal proteinuria, which is probably caused by trauma induced by cystocentesis, as blood contamination within the urine sample may also contribute to proteinuria (Pieche and Wycislo, 2019). In fact, one to three traces of blood were also found in the urine samples of four dogs (three males and one female) in the present study. However, protein (P=0.79) and blood (P=0.64) detection in the urine did not differ between time points and should not be associated with TK use (Table 2). In a previous study on dogs treated with oral NSAIDs for 90 consecutive days, the urine density, pH, and protein levels remained within the reference range (Luna *et al*., 2007).

The UPC ratio accounts for variations in urine volume throughout the day based on creatinine concentration. The UPC values correlated well with the 24-hour urine protein excretion in dogs (Pieche and Wycislo, 2019; Sant'Anna *et al.*, 2019). Therefore, UPC was assessed in the present study, and our results showed that such parameters remained within the normal range for dogs and did not change significantly from baseline to day 30 (P=0.38) (Table 2). In another study, the UPC of cats was also normal, and it did not change after seven days of continuous instillation of diclofenac ophthalmic solution (Hsu *et al*., *et al*., 2015). GFR is another useful test to evaluate the progress of renal insufficiency and nephropathies, even in the early stages (Hsu *et al*., 2015; Fusellier *et al.*, 2008). One experimental study conducted in cats suggested that topical application of diclofenac as an ophthalmic solution might be associated with reduced GFR; however, the findings were confusing, as decreased GFR was associated with iatrogenic hypovolemia due to repeated blood collection (Hsu *et al.*, 2015). In contrast, in a study in which dogs received oral meloxicam, GFR remained normal after seven consecutive days of treatment (Fusellier *et al.*, 2008). Considering that the dogs were kept in the hospital for no longer than a day for blood collection, GFR could not be evaluated in the current study.

In the present study, instillation of NSAIDs did not induce changes in serum potassium levels (P=0.06). In contrast, the sodium levels increased significantly on days 15 and 30 compared to the baseline (P<0.01) (Table 1). However, these values remained within the reference range at all time points, and such fluctuations were probably unrelated to TK use (Table 1). In two studies on dogs treated with different oral NSAIDs for seven consecutive days, the serum levels of sodium and potassium did not change significantly between the control and treatment groups (Fusellier *et al.*, 2008; Borges *et al.*, 2013).

Throughout the study period, the serum total protein levels remained constant and within the reference range for dogs (P=0.06) (Table 1). Albumin levels also remained within the reference range during the study; however, in comparison with baseline, significantly higher albumin levels were observed on day 15 (P<0.001) (Table 1). The total protein and albumin levels also did not change significantly in cats and chickens treated with the ophthalmic solution diclofenac for over seven days (Hsu *et al*., 2015. Griggs *et al*., 2017). However, significantly lower albumin levels were observed in chickens that received topical diclofenac for seven days. In a study by Griggs *et al.* (2017), although the albumin levels remained within the reference range for chickens, the authors could not conclude whether this finding was associated with glomerulonephritis.

Another limitation of the current study is that it did not investigate the occurrence of fecal occult blood, as long-term administration of oral NSAIDs may cause gastric lesions (Luna *et al.*, 2007; Dobberstein *et al.*, 2022). Further, 82% and 63% of dogs with perforated gastrointestinal ulcers had vomiting and anorexia, respectively (Dobberstein *et al.*, 2022). However, vomiting, anorexia, and melena were not observed in any of the dogs throughout the study.

Serum lactate levels have been used to predict the severity of illness and the risk of mortality in many conditions, such as infections, trauma, cancer, organ disease, and sepsis (Mooney *et al*., 2014; Franco *et al*., 2016). Studies have demonstrated that serum lactate levels are associated with prognosis in patients with upper gastrointestinal bleeding (Shah *et al*., 2014; El-Kersh *et al*., 2015; Ko *et al*., 2015; Lee *et al*., 2017). One of these studies demonstrated that higher lactate levels within 24 hours after admission were associated with more frequent re-admissions over the next 7 days and a higher 30-day mortality rate (Lee *et al*., 2017). In veterinary medicine, hyperlactatemia is associated with varying degrees of hypoperfusion and is often used as a prognostic indicator in dogs with gastric dilatation-volvulus (Mooney *et al.*, 2014; Verschoof *et al*., 2015). Another study showed that neutrophilia with a left shift and hyperlactatemia were the most common hematological (83.3%) and biochemical abnormalities (54.5%) found in dogs with gastroduodenal ulcers associated with oral administration of NSAIDs (Dobberstein *et al.*, 2022). Therefore, the assessment of lactate levels in dogs in the current study may be considered an indirect method to evaluate possible lesions in the gastrointestinal tract. In dogs weighing 1–26 kg, the levels of lactate range from 2.0 to 3.9 mmol/L, as determined by the same portable lactimeter used herein (Franco *et al*., 2016). The lactate levels were normal and did not change during the study (P=0.37) (Table 1).

CONCLUSIONS

Based on our observations, instillation of TK every 12 h for 30 consecutive days does not cause clinically relevant changes in the blood count, biochemical profile, or urinalysis of healthy dogs.

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