http://dx.doi.org/10.1590/1678-4162-10219

F.Q. Pereira
https://orcid.org/0000-0003-3854-0638
B. Santos
https://orcid.org/0000-0002-5022-5422
T. Carboni
https://orcid.org/0000-0001-7523-4803
M. Bender
https://orcid.org/0000-0002-0285-2296
A.C.B. Cunha
https://orcid.org/0000-0002-0989-8406
M.G. Biajoli
https://orcid.org/0000-0002-4345-178X
F.B. Mello
https://orcid.org/0000-0002-2787-1768
P.R. Silva
https://orcid.org/0000-0002-1712-7046
J.A.T. Pigatto
https://orcid.org/0000-0002-1541-9133
J.R.B. Mello
https://orcid.org/0000-0002-7120-7709

***Arq. Bras. Med. Vet. Zootec.*, v.71, n.6, p.1865-1872, 2019**

Systemic absortion and adverse effects of topical ocular use of ketorolac tromethamine and sodium diclofenac in New Zealand rabbits for 90 days

[*Absorção sistêmica e efeitos adversos do uso tópico ocularpor 90 dias de cetorolaco de trometamina e diclofenacode sódio em coelhos da raça Nova Zelândia*]

F.Q. *Pereira*[1], B. *Santos*[2], T. *Carboni*[2], M. *Bender*[3], D. *Driemeier*[1], A.C.B. *Cunha*[4], M.G. *Biajoli*[4], F.B. *Mello*[4], P.R. *Silva*[5], J.A.T. *Pigatto*[1], J.R.B. *Mello*[3]

[1]Faculdade de Medicina Veterinária - Universidade Federal do Rio Grande do Sul - Porto Alegre, RS
[2]Programa de pós-graduação - Universidade Federal do Rio Grande do Sul - Porto Alegre, RS
[3]Programa de pós-graduação - Universidade Federal do Paraná - Curitiba, PR
[4]Universidade Federal de Ciências da Saúde de Porto Alegre - Porto Alegre, RS
[5]Programa de graduação - Universidade Federal de Ciências da Saúde de Porto Alegre - Porto Alegre, RS

ABSTRACT

The effect of the systemic absorption of 0.1% diclofenac sodium (DS) eyedrop was compared to that of 0.5% ketorolac tromethamine (KT) in female New Zealand white rabbits treated on both eyes three times a day for 90 days. The rabbits were divided in three groups of six animals (n= 18): KT group, DS group, and control (Co) group, in which saline (0.9% NaCl) solution was instilled. Water and food consumption were measured daily, clinical examination was performed weekly, and blood samples were collected every 30 days for laboratory examination. The plasma was analyzed for the presence of KT and DS by solid-phase extraction (SPE) associated with mass spectrometry (MS). Systemic absorption of these drugs was confirmed by SPE-MS, allowing their separation and identification in the plasma. At the end of the treatment, the animals were euthanized and necropsied, and no macroscopic or microscopic changes were found. This observation confirmed the laboratory results, which were within normal reference standards for the species. According to the results obtained, it can be concluded that treatment with eyedrops containing KT and DS for 90 days in healthy rabbits does not cause adverse systemic effects.

Keywords: rabbits, eyedrops, NSAID, systemic absorption

RESUMO

Comparou-se o efeito da absorção sistêmica do colírio de diclofenaco de sódio 0,1% (DS) em relação ao de cetorolaco de trometamina 0,5% (CT) em coelhas da raça Nova Zelândia, tratadas nos dois olhos, três vezes ao dia, por 90 dias. As coelhas foram separadas em três grupos de seis animais (n=18): grupo CT, grupo DS e grupo controle (Co), no qual foi instilada solução fisiológica (NaCl 0,9%). Os consumos de água e ração foram mensurados diariamente, os exames clínicos foram realizados semanalmente e o sangue foi coletado a cada 30 dias para realização de exames laboratoriais. O plasma foi analisado para detectar a presença de CT e DS por extração em fase sólida (SPE) associada à espectrometria de massas (MS). A absorção sistêmica desses fármacos foi confirmada por SPE-MS, permitindo sua separação e identificação no plasma. Ao final do tratamento, os animais foram eutanasiados e necropsiados, e não foram encontradas alterações macroscópicas ou microscópicas. Essa observação confirmou os resultados laboratoriais, que estavam dentro dos padrões de referência para a espécie. De acordo com os resultados obtidos, pode-se concluir que o tratamento com colírio contendo KT e DS, por 90 dias, em coelhos saudáveis, não causa efeitos adversos sistêmicos.

Palavras-chave: coelhos, colírio, AINE, absorção sistêmica

Recebido em 1 de agosto de 2017
Aceito em 27 de março de 2019
E-mail: fabianaquartiero@hotmail.com

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drug classes worldwide. They are used in humans and animals for the purpose of symptomatic relief of pain and acute or chronic inflammatory conditions (Jericó and Andrade, 2008). Inhibition of the cyclooxygenase 1 and 2 (COX-1/COX-2) enzymes promotes anti-inflammatory and analgesic action (Jericó and Andrade, 2008; Tasaka, 2011). The type of NSAID, COX-1 or COX-2 selectivity, half-life elimination, and treatment time are the main factors that trigger adverse effects in humans and animals (Jericó and Andrade, 2008). In animals, the main adverse effects of NSAIDs are well documented: gastric disorders, blood dyscrasia, hypoproteinemia, bronchial constriction, hepatic diseases, renal toxicity, and fetal abnormalities (Giuliano, 2004; Jericó and Andrade, 2008; Sparkes *et al*., 2010; Lanuza *et al*., 2015). Systemic side effects may also occur when drugs are delivered in the form of eye drops since their absorption occurs in the conjunctiva and nasal mucosa. Therefore, attention should be given to patients at the extreme ages, especially in neonates and young individuals, since they are more drug sensitive than adults for the following reasons: immature hepatic enzyme system, low weight and lower blood volume. Due to these reasons, medication may lead to serious adverse events, including death (Bowman *et al*., 2004; Levy and Zadok, 2004; Kim *et al*., 2010; Vita Sobrinho and Batistuzzo, 2010; Tasaka, 2011; Hsu *et al*., 2015).

Although topical corticosteroids and topical NSAIDs are widely used by veterinary ophthalmologists, corticosteroids have additional actions that can be detrimental to the management of ocular disease (Giuliano, 2004). These steroids increase the risk of corneal infection, potentiate corneal collagenase activity, and their prolonged use may develop cataract and cause increasing intraocular pressure (Giuliano, 2004; Kim *et al*., 2010). In the case of diabetic patients, the use of NSAIDs is mandatory since opical corticosteroids may interfere with glycemic control (Abraham *et al*., 2011; Bahar *et al*., 2011). Frequently, veterinary ophthalmologists use NSAIDs to treat patients with uveitic conditions, for which corticosteroids are contraindicated (Giuliano, 2004), as well as to control inflammation and pain in patients with keratitis and after corneal surgery (Giuliano, 2004; Hsu *et al*., 2015; Lanuza *et al*., 2015). In many conditions, ocular surface inflammation requires prolonged treatment, as in humans with allergic keratoconjunctivitis. In these cases, NSAIDs are a better option than steroids (Leonardi *et al*., 2012). Atopic dogs with ocular signs are also benefited by analgesia induced by topical NSAIDs (Giuliano, 2004; Leonardi *et al*., 2012). Ketorolac tromethamine (0.5%) is the only ophthalmic NSAID currently approved by the FDA for the relief of ocular itching in seasonal allergic conjunctivitis in humans. Other NSAIDs, such as diclofenac, may also have some effect in controlling the acute symptoms of allergic conjunctivitis (Kim *et al*., 2010). These drugs should be used cautiously in patients with a history of NSAID intolerance (Leonardi *et al*., 2012; Tan and Hsu, 2016). However, despite the low incidence of NSAID intolerance, important adverse effects have been reported with the use of ophthalmic NSAIDs, such as corneal collagen destruction (Esteroideos, 2009) and corneal perforation (Demirel and Sarac, 2012). The presence or absence of these effects depend on the individual's drug tolerance (Levy and Zadok, 2004; Vita Sobrinho and Batistuzzo, 2010; Leonardi *et al*., 2012). There are reports of asthma exacerbation in adults after topical ocular use of diclofenac (Sharir, 1997; Leonardi *et al*., 2012; Tan and Hsu, 2015) and ketorolac (Sitenga *et al*., 1996; Leonardi *et al*., 2012).

Topical NSAIDs for humans have been used extralabel in animals for inflammatory eye conditions, such as keratitis and uveitis. Extralabel use in animals increases the risk of adverse reactions, which are exacerbated, reduced, or even different from those expected for certain drugs (Hsu *et al*., 2015). Identifying the susceptibilities of each species to these drugs is a challenge, due to the inter and intra-species peculiarities such as anatomical, physiological, genetic and even behavioral differences (Tasaka, 2011). In veterinary ophthalmology, the challenge is even greater, because these patients of different sizes and weights receive the same dose of drug when a drop of ophthalmic solution is instilled (Vita Sobrinho and Batistuzzo, 2010; Hsu *et al*, 2015). In this study, the rabbit was chosen as the experimental model due to its small size and the anatomical similarities with the cornea of other animal species such as dogs,

cats, rats, monkeys, and humans (Dougth, 1990). We also aim to observe it as an individual, since rabbits directed to the production of companion animals have grown in recent years. The aim of this study was to investigate the potential adverse effects of a 90-day treatment with eyedrops containing 0.1% diclofenac sodium and 0.5% ketorolac tromethamine, which were prepared without the use of preservatives.

MATHERIAL AND METHODS

The animals were selected after general and ophthalmological evaluation, and laboratory analysis of the blood profile. Healthy New Zealand white female rabbits (n= 18; age: 90 days; weight range: 2.0-2.5kg) were selected for this study. The animals were kept in individual stainless-steel cages in a *vivarium* of the Veterinary Hospital (Federal University of Rio Grande do Sul), where they were fed a standardized diet and could drink water *ad libitum*. There, a 12h light-dark cycle (from 8:30 am to 8:30pm) was provided in an environment of constant relative humidity (RH; 50%) and temperature (20°C). The study was initiated after approval by the Ethics Committee on Animal Use (CEUA) of the Federal University of Health Sciences (UFCSPA), Porto Alegre, BR, and began after a seven-day adaptation period. Rabbits (n= 18) were randomly divided into three treatment groups (n= 6/animal each), and both eyes were treated with eyedrops, three times per day, for 90 consecutive days.

Each group received one drop (0.028mL) of the following solutions: ketorolac tromethamine (Ophthalmos, Brazil; 0.5%; 0.143mg/drop), diclofenac sodium (Ophthalmos, Brazil; 0.1%; 0.036mg/drop), and 0.9% sodium chloride. The eyedrops were prepared without preservatives: sodium chloride, purified water, and hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4. Water and food intake were measured daily for each subject. Weight control was performed weekly, assessing the state of alertness, color of mucous membranes and surface of the eyes. The corneas and eye attachments of all groups were evaluated weekly by biomicroscopy with a slit lamp (Kowa® SL-15 Slit-lamp Biomicroscope, Japan). Complete ophthalmic examination with the Schirmer's tear, green lissamine, and fluorescein tests and aplanation tonometry (Tonopen® Avia, Reichert Technologies, USA) was performed only on admission to avoid any interference in the study. Qualitative parameters of the clinical examination were interpreted using an empirical system through crosses (Table 1).

Table 1. Qualitative parameters of the weekly general and ophthalmologic evaluation

Weekly Exam	-	+	++	+++
Alertness	Alert	Apathy	Stupor	Coma
Mucosal staining	Normal	Pale	Congested	Cianotyc
Blepharospasm	Absent	Sporadic	Constant	Intense
Ocular secretion	Absent	Mild	Moderate	Intense
Ocular hyperemia	Absent	Mild	Moderate	Intense

Blood samples were collected on admission and taken at zero, 30, 60, and 90 days of treatment for the following laboratory tests (white blood cell and platelet count, prothrombin and thromboplastin times, total protein, albumin, creatinine, and sodium and potassium ions) and mass spectrometry analysis (solid-phase extraction (SPE) and mass spectrometry detection using positive-mode electrospray ionization (ESI(+)-MS) by to identify NSAIDs in the plasma.

RESULTS AND DISCUSSION

Systemic adverse effects may also occur with using NSAIDs in the form of eyedrops. A fraction of a topically applied ophthalmic medication will be systemically absorbed through the conjunctiva or episclera, and nasolacrimal system (Sasaki *et al*., 1996; Hsu *et al*., 2015; Lanuza *et al*., 2015). Systemic absorption of eyedrops containing NSAIDs was demonstrated using analytical methodology (SPE-ESI(+)-MS). The solid-phase extraction (SPE) is currently one of the most used

chromatographic techniques for clean up, extraction, and/or concentration of analytes. The mass spectrometry (MS) is an extremely valuable analytical technique by which atoms and molecules are analyzed for molecular masses. This accurate information on the molecular mass is sufficient to identify a chemical compound. The use of ESI(+)-MS allows neutral molecules of an analyte to be converted into the ionic form after undergoing various combinations of electric and magnetic fields in vacuum (Lanças, 2009).

In this study, SPE was used to separate specific molecules for the sole purpose of cleaning the blood sample, and the MS was used only to identify the active principle in given periods. Methodologies for quantification of analytes at low concentrations would require a long time of analytical development and were not within the objectives of this study. The chemical formulas of diclofenac sodium and tromethamine ketorolac are as follows: $C_{14}H_{10}Cl_2NNaO_2$ (MW: 318.1g/mol) and $C_{15}H_{13}NO_3C_4H_{11}NO_3$ (MW: 376.4g/mol), respectively. Given the methodology used in this study, the analytes were detected in the positive-mode analysis of ESI (+). The 318(+) ion for diclofenac was qualitatively detected in blood samples corresponding to 60 and 90 days of treatment of the DS group. The 256(+) ion for ketorolac was detected qualitatively only in blood samples corresponding to 90 days of treatment of the KT group. Diclofenac was detected in the plasma on days 60 and 90, whereas ketorolac was detected only on day 90 of treatment. This may have occurred because balance in the distribution between various body compartments depends on the drug's ability to cross tissue barriers, its pK_a, blood sample pH, whether it is in the bound or free form, and on tissue-water partition coefficient. The 0.5% KT and 0.1% DS solutions are different in concentration, chemical structures, molecular weights, lipophilicty, and pK_a values (Abib, 2008; Florio and Sousa, 2011).

Systemic adverse effects of NSAIDs occur primarily by COX-1/COX-2 selectivity non-steroidal antiinflamatory drugs, and may also have other antiinflammatory effects besides COX inhibition, including suppression of polymorphonuclear and blockade of platelet aggregation by thromboxane inhibition. Gastritis, gastric ulcers, gastroenteritis, and renal failure are the most common adverse effects of COX-1 inhibition (Jericó and Andrade, 2008; Kim *et al*., 2010; Sparkes *et al*., 2010; Tasaka, 2011; Satoh *et al*., 2013). In animals, the main adverse effects of NSAIDs are well documented: gastric disorders, blood dyscrasia, hypoproteinemia, bronchoconstriction, hepatic diseases, renal toxicity, and fetal abnormalities (Giuliano, 2004; Lanuza *et al*., 2015). Local adverse effects have also been reported with the use of ophthalmic NSAIDs, such as corneal collagen destruction (Esteroideos, 2009) and corneal perforation (Demirel and Sarac, 2012).

In the present study, rabbits showed no clinical or laboratory changes after 90 days of treatment with 0.1% DS and 0.5% KT eyedrops. Changes in alertness or color of mucous membranes, blepharospasm, ocular secretion, or conjunctival hyperemia were not observed. No statistically significant difference was found between groups regarding blood count, leukogram, platelet count, prothrombin and thromboplastin times, total protein, albumin, creatinine, and sodium and potassium ions. Water and food intake and weight gain of animals were not statistically different between groups (Table 2). Animal weight showed an average increase throughout the treatment, although independent of the group (Figure 1). According to Jepson (2010), weight control is one of the main parameters of clinical evaluation in rabbits.

Regarding results of autopsies, all microscopic lesions observed in the animals were nonspecific and characterized by mild-to-moderate hepatic, renal, and gastric submucosal congestion. Such lesions were found in the three groups and are a common finding in euthanized animals because acute passive congestion occurs in the vascular system after a sudden interruption of venous return (Figure 2).

Table 2. Water and food intake and animal weights in each group and time points. Weight gain of animals and results of the comparative analysis

	Groups **			Value -P ***		
Variables/Times	Co	DS	KT	Group	Time	Interaction
Water consumption(mL)*				0.506	0.479	0.434
30 days	349±50	331±70	334±51			
60 days	387±51	436±36	385±69			
90 days	376±47	415±36	407±32			
Food consumption (g)*				0.097	0.174	0.886
30 days	187±44	222±34	209±43			
60 days	199±35	210±5	197±26			
90 days	181±38	231±32	222±10			
Weight (Kg)				0.459	<0.001	0.055
Initial	3.1±0.5	2.8±0.3	2.6±0.2			
End	4.7±0.5	4.7±0.4	4.6±0.3			
Weight gain (Kg)	1.6±0.4	1.9±0.2	2.1±0.2	0.291		

*Results adjusted for Initial weight; **N= 6 in all groups; ***ANOVA testa t a 5% significance level.

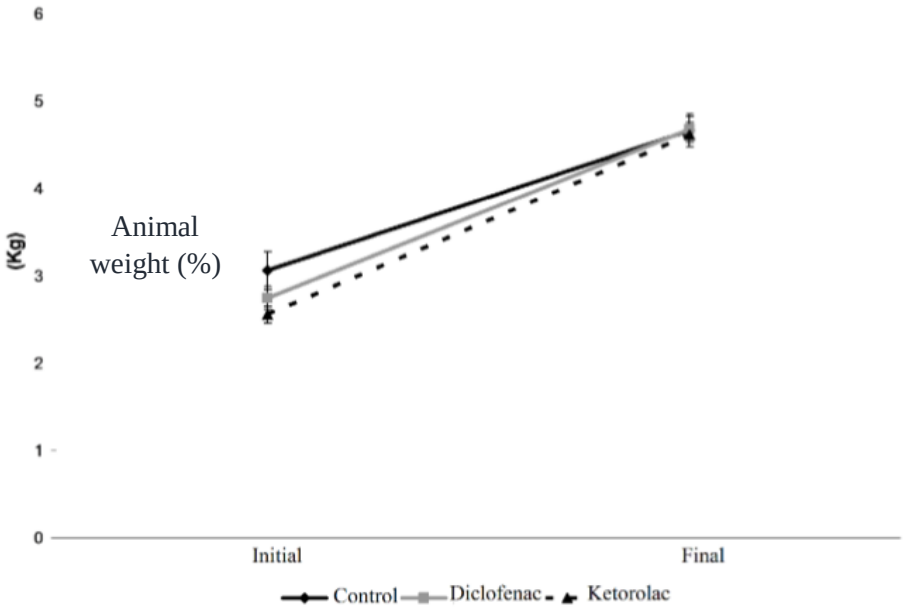

Figure 1. Weight gain of animals compared between groups and times. The repeated measures, with two factors, were analyzed (ANOVA) using the initial weight as covariate. The animals exhibited a linear weight gain (P< 0.001) regardless of the group.

Only one rabbit of the KT group, which had a sudden death on the 45th day of treatment, showed nonspecific changes, such as pulmonary edema and liver congestion. This rabbit had no indications of parasitic, gastric, kidney, or heart problems. The cause of its death was inconclusive, given that it was gaining weight at a rate similar to that of other animals, and no change was observed in the weekly clinical examination. However, it is known that anaphylactic and anaphylactoid reactions may occur with the use of NSAIDs, including eyedrops (Sitenga *et al*., 1996; Sharir, 1997; Risser *et al*., 2009; Sánchez-Borges *et al*., 2010; Kumar *et al*., 2015). NSAID-induced drug allergy occurs sporadically in both children and adult humans. Such an allergy is not a true allergy (it is not an IgE event), as there is a

potential for cross sensitivity to acetylsalicylic acid, phenyl acetic acid derivatives, and other NSAIDs. All these drugs share the same mechanism of COX-1 inhibition in the prostaglandin synthesis pathway (Risser *et al*., 2009; Kumar *et al*., 2015; Tan and Hsu, 2016). According to the World Allergy Organization update (2014), aspirin, and other analgesic and antipyretic drugs are among those most frequently involved in allergic drug reactions. Therefore, being aware of the history of aspirin allergy, avoiding such adverse events is mandatory whenever ketorolac is prescribed to patient (Kumar *et al*., 2015). NSAID-triggered bronchoconstriction can be serious and often fatal in susceptible individuals (Sitenga *et al*., 1996; Sharir, 1997; Sánchez-Borges *et al*., 2010; Torres *et al*., 2014; Tan and Hsu, 2016). However, the hypothesis that the rabbit may have suffered a delayed hypersensitivity to ketorolac could not be confirmed.

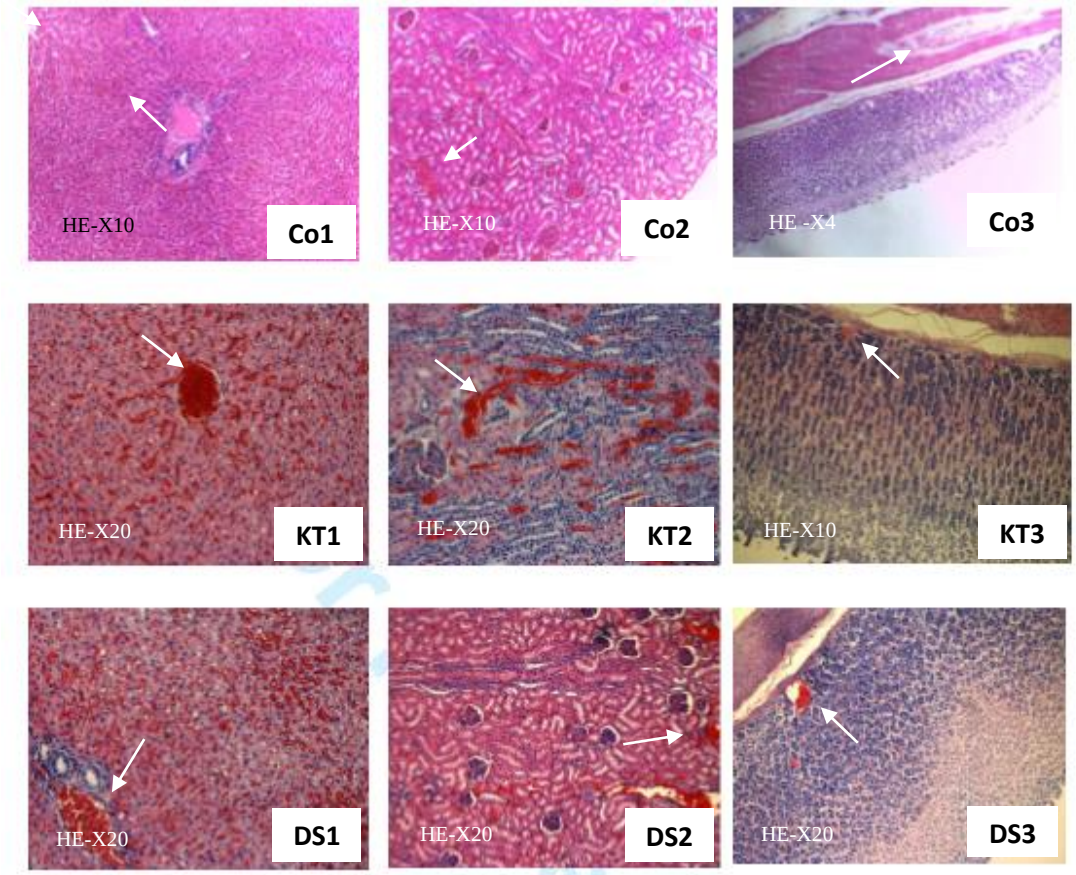

Figure 2. Hepatic (1), renal (2), and gastric (3) histopathology of animals: the control (Co), ketorolac (KT), and diclofenac (DS) groups. All microscopic lesions are nonspecific and characterized by mild-to-moderate hepatic, renal, and gastric submucosal congestion (white arrow). Hematoxylin-Eosin (HE). Sample collected in december 2015.

CONCLUSION

Absortion of diclofenac sodium occurs in the conjunctival and nasal mucosa of rabbits. The SPE-MS analytical methodology was effective in qualitatively detecting these NSAIDs in the plasma of rabbits. Diclofenac sodium was detected on days 60 and 90, and ketorolac tromethamine detected only on day 90 of treatment. No local or systemic adverse effects were observed. This study showed that ophthalmic instillation of 0.5% ketorolac tromethamine or 0.1% diclofenac sodium, three times a day for 90 days, is well tolerated in healthy rabbits.

REFERENCES

ABRAHAM, G.; ALLERSMEIER, M.; SCHUSSER, G.F.; *et al*. Serum thyroid hormone, insulin, glucose, triglycerides and protein concentrations in normal horses: association with topical dexamethasone usage. *Vet. J*., v.188, p.307-312, 2011.

ABIB, F.C. *Terapêutica farmacológica em oftalmologia*. Rio de Janeiro: Cultura Médica, 2008. p.384-386.

BAHAR, I.; VINKER, S.; KAISRMAN, I. The effect of topical steroids on blood glucose profile in diabetic patients. *J. Clin. Exp. Ophthalmol*., v.2, p.1-3, 2011.

BOWMAN, R.J.C.; COPE, J.; NISCHAL, K.K. Ocular and systemic side effects of brimonidine 0.2% eye drops (Alphagan) in children. *Eye*, v.18, p.24, 2004. Available in: <http://www.nature.com/eye/journal/v18/n1/full/6700520a.html>. Accessed in: 22 Feb. 2016.

DEMIREL, S.; SARAC, O. Late corneal perforation with topical diclofenac sodium use after radiotherapy. *Eye Contact Lens*, v.38, p.197-199, 2012.

DOUGHTY, M.J. Morphometric analysis of the surface cells of rabbit corneal epithelium by scanning electron microscopy. *Am. J. Anat*., v.189, p.316-328, 1990.

ESTEROIDEOS, R. Corneal melting and topical nonsteroidal anti-inflammatory drug (NSAID). *Arch. Soc. Esp. Oftalmol.*, v.84, p.311-314, 2009.

FLÓRIO, J.C.; SOUSA, A.B. Farmacocinética. In: SPINOSA, H.S. *et al*. *Farmacologia aplicada à medicina veterinária*. Rio de Janeiro: Guanabara Koogan, 2011. p.33-35.

GIULIANO, E.A. Nonsteroidal anti-inflammatory drugs in veterinary ophthalmology. *Vet. Clin. N. Am. Small. Anim. Pract*., v.34, p.707-19, 2004. Available in: <http://www.geac.ufv.br/aines.pdf>. Accessed in: 10 Oct. 2015.

HSU, K.K.; PINARD, C.L.; JOHNSON, R.J. *et al*. Systemic absorption and adverse ocular and systemic effects after topical ophthalmic administration of 0.1% diclofenac to healthy cats. *Am. J. Vet. Res*., v.76, p.253-265, 2015. Available in: <http://avmajournals.avma.org/doi/abs/10.2460/ajvr.76.3.253>. Accessed in: 15 Nov. 2016.

JEPSON, L. *Coelhos*. In:_____. *Clínica de animais exóticos*. Rio Janeiro: Elsevier, 2010. 45p.

JERICÓ, M.M.; ANDRADE. S.F. Antiinflamatórios. In: ANDRADE, S.F. *Manual de terapêutica veterinária*. São Paulo: Roca, 2008. 121-123p.

KIM, S.J.; FLACH, A.J.; JAMPOL, L.M. Nonsteroidal anti-inflammatory drugs in ophthalmology. *Surv. Ophthalmol*., v.55, p.108-33, 2010. Available in: <http://www.surveyophthalmol.com/article/S0039-6257(09)00191-X/pdf>. Accessed in: 9 Mar. 2013.

KUMAR, H.; KAVYA, G.; SHUBHA, R. Ketorolac eye drop induced allergic wheal and chemosis. *Int. J. Basic. Clin. Pharmacol*. v.4, p.808-810, 2015. Available in: <http://imsear.li.mahidol.ac.th/bitstream/123456789/165188/1/ijbcp2015v4n4p808.pdf>8. Accessed in: 3 Nov. 2016

LANÇAS, F.M. A cromatografia líquida moderna e a espectrometria de massas: finalmente "compatíveis". *Sci. Chromatograph*., v.1, p.35-61, 2009. Available in: <http://scientiachromatographica.com/files/v1n2/v1n2a4.pdf>. Accessed in: 5 Feb. 2013.

LANUZA, R.; RANKIN, A.J.; KUKANICH, B.; MEEKINS J.M. Evaluation of systemic absorption and renal effects of topical ophthalmic flurbiprofen and diclofenac in healthy cats. *Vet. Ophthalmol*., v.19, p.24-29, 2015. Available in: <http://www.vetweb.com.br/newgaleria/gallery/admin/rest/arquivos_agenda/Lanuza_et17 _al-2016-Veterinary_Ophthalmology.pdf>. Accessed in: 20 Nov. 2016.

LEONARDI, A.; BOGACKA, E.; FAUQUERT, J.L.; *et al*. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy*, v.67, p.1327-1337, 2012. Available in: <http://onlinelibrary.wiley.com/doi/10.1111/all.12009/epdf>. Accessed in: 30 Oct. 2016.

LEVY, Y.; ZADOK, D. Systemic side effects of ophthalmic drops. *Clin. Pediatr.*, v.43, p.99, 2004. Available in: <http://cpj.sagepub.com/content/43/1/99.full.pdf+html>. Accessed in: 11 Nov. 2013.

RISSER, A.; DONOVAN, D.; HEINTZMAN, J.; PAGE, T. NSAID prescribing precautions. *Am. Fam. Physician*, v.80, p.1371-1378, 2009. Available in: <https://www.researchgate.net/profile/John_Heintzman/publication/40678294_NSAID.prescribing_precautions/links/53fb7cdb0cf22f21c2f32fdb.pdf>. Accessed in: 06 Nov. 2016.

SÁNCHEZ-BORGES, M.; CABALLERO-FONSECA, F.; CAPRILES-HULETT, A.; GONZALEZ-AVELEDO, L. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs: an update. *Pharmaceuticals*, v.3, p.10-18, 2010. Available in: <http://www.mdpi.com/1424-8247/3/1/10/htm>. Accessed in: 11 Jun. 2016.

SASAKI H.; ICHIKAWA, M.; KAWAKAMI; S. *et al*. In situ ocular absorption of tilisolol through ocular membranes in albino rabbits. *J. Pharmacol. Sci.*, v.85, p.940-943, 1996.

SATOH, H.; AMAGASE, K.; EBARA, S. *et al*. Cyclooxygenase (COX)-1 and COX-2 both play an important role in the protection of the duodenal mucosa in cats. *J. Pharmacol. Exp. Ther*., v.344, p.189-195, 2013. Available in: <http://jpet.aspetjournals.org/content/344/1/189.full>. Accessed in: 15 Nov 2016.

SHARIR, M. Exacerbation of asthma by topical diclofenac. *Arch. Ophthalmol*., v.115, p.294-295, 1997.

SITENGA, G.L.. Asthma caused by topical application of ketorolac. *Ophthalmology*, v.103, p.890-892, 1996.

SPARKES, A.H.; HEIENE, R.; LASCELLES, B.D.X., *et al*. ISFM and AAFP consensus guidelines: long-term use of 13 NSAIDs in cats. *J. Feline Med. Surg*., v.12, p.521-538, 2010. Available in: <https://www.researchgate.net/profile/Polly_Taylor2/publication/4510120155_ISFM_and_AAFP_consensus_guidelines_longterm_use_ofNSAIDs_in_cats/links/0916e41505c57f38aa9b000000.pdf>. Accessed in: 3 May 2016.

TAN, J.H.Y.; HSU, A.A.L. Nonsteroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease phenotype: Topical NSAID and asthma contro l– A possible oversight link. *Resp. Med.*, v.118, p.1-3, 2016.

TASAKA, A.C. Antiinflamatórios não esteroidais. In: SPINOSA H.S. *Farmacologia aplicada à medicina veterinária*. 5.ed. Rio de Janeiro: Guanabara Koogan, 2011. cap. 21

TORRES, M.J.; BARRINUEVO, E.; KOWALSKI, M.; BLANCA, M. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. *Immunol. Allergy Clin. N. Am.* v.34, p.507-524, 26 2014.

VITA SOBRINHO, J.B.; BATISTUZZO, J.A.O. Iatrogenia ocular. In: NAKANAMI, C.R. *et al*. *Oftalmopediatria*. São Paulo: Roca, 2010. p.587-588.