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Effects of meloxicam administered by different routes to control experimental uveitis in dogs

Efeitos do meloxicam, aplicado por diferentes vias, no controle de uveíte experimental em cães

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ABSTRACT

Efficacy of meloxicam, administered by different routes was studied in experimental uveitis in dogs. Anterior chamber paracentesis was accomplished at two different moments (M0 and M1), with a five hour interval among them. At M0 and M1, 0.2mL of aqueous humor was collected and total protein and prostaglandin E₂ (PGE₂) quantitation was determined. Four groups were formed (n=5), which received meloxicam at the end of M0, by the following routes: subcutaneous (GIm), subconjunctival (GII), and topical (GIII). A fourth group that received no treatment was instituted (Control). Conjunctival histopathology of the GII was performed. Results were evaluated statistically (P≤0.05). In all groups, protein and PGE₂ values enhanced significantly in M1. Protein and PGE₂ values did not change significantly between groups at M1. Inflammatory exudate of acute character and mild hemorrhage were seen at histopathology, after meloxicam administration. Meloxicam were unable to inhibit PGE₂ synthesis and the protein influx to the anterior chamber by any of the tested routes.

Key words: uveitis, meloxicam, total protein, prostaglandin E₂, dogs.

RESUMO

Foram estudados os efeitos do meloxicam, aplicado por diferentes vias, em uveítes experimentais em cães. Realizou-se paracentese de câmara anterior em dois momentos (M0 e M1), com intervalo de cinco horas entre si. Em M0 e M1, foram coletados 0,2mL de humor aquoso e determinou-se a concentração de proteína total e de prostaglandina E₂ (PGE₂). Constituíram-se quatro grupos (n=5), que receberam meloxicam ao final de M0 pelas vias subcutânea (GI), subconjuntival (GII) e tópica (GIII). Um quarto grupo não recebeu tratamento (Controle). Procedeu-se à avaliação

histopatológica nos indivíduos do GII. Os resultados foram avaliados estatisticamente (p≤0,05). Em todos os grupos, encontrou-se aumento significativo dos níveis protéicos e de PGE₂ em M1. Não se observou diferença significativa, em M1, entre os grupos para nenhum dos parâmetros estudados. Exsudado inflamatório de caráter agudo e hemorragia discreta foram vistos à histopatologia após a aplicação do meloxicam. O meloxicam foi ineficaz em inibir a síntese de PGE₂ e o influxo de proteínas para a câmara anterior, por qualquer uma das vias testadas.

Palavras chave: uveíte, meloxicam, proteína total, prostaglandina E₂, cães.

INTRODUCTION

Anterior uveitis is defined as the inflammation of the iris and ciliary body. The condition courses with most of the intraocular diseases, due to the highly vascular nature of uvea and its contiguity with other structures of the eye (COLLINS & MOORE, 1999). Numeral infectious and noninfectious diseases can cause anterior uveitis (van der WOERDT, 2001).

The anterior segment of the eye has a selective barrier (blood-aqueous barrier), which controls the flux between the blood current and the primary aqueous humor (GUM et al., 1999). The integrity of the blood-aqueous barrier depends on tight junctions, located at the nonpigmented epithelium of the ciliary body, which controls the influx of aqueous fluid to the posterior chamber. This barrier is disrupted

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in anterior uveitis, resulting in the exudation of plasma proteins and cellular components into the anterior chamber, what can be detected clinically as aqueous flare. Such events are responsible for secondary aqueous humor formation. Prostaglandins (PGs) are considered the most important chemical mediators in the scope of intraocular inflammation (MILLICHAMP et al., 1991; DIZIEZYC et al., 1992; ROZE et al., 1996; COLLINS & MOORE, 1999; GILMOUR & LEHENBAUER, 2006).

Uveitis are managed by topical instillation of mydriatics and cycloplegics associated with topically and systemically administered steroidal and/or nonsteroidal anti-inflammatory drugs, associated with the treatment of the underlying disease (van der WOERDT, 2001). Fibrinolytics agents may be useful when blood clots and cellular debris are present (COLLINS & MOORE, 1999). Subconjunctival administration of anti-inflammatory drugs is an alternative route when markedly inflammation is present, once this route delivers higher levels of medication to the eye for an extended period of time (HOLMBERG & MAGGS, 2004).

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered in uveitis (WARD, 1996; KROHNE et al., 1998; GIULIANO, 2004; GILMOUR & LEHENBAUER, 2006). Their use is preferable upon corticosteroids in diabetic animals and in those with systemic diseases (GIULIANO et al., 2004; MASSA et al., 2002). In addition, NSAIDs are recommended due to their ability to prevent miosis formation (MILLICHAMP et al., 1991; 1992; KROHNE et al., 1998).

Meloxicam is a nonnarcotic NSAID of the acidic enolcarboxamide class (BUSCH et al., 1998). It has a high intrinsic activity combined with a low ulcerogenic potential (LUNA et al., 2007) and minimally affects platelet function in dogs (BENJAMIN et al., 2007). Meloxicam is 12 times more effectively in inhibiting COX-2 activity than COX-1 (KAY-MUGFORD et al., 2000). Several studies proved that the agent has good anti-inflammatory and analgesic properties (DENEUCH et al., 2004; PETERSON & KEEFE, 2004; CAULKETT et al., 2003; LAFUENTE et al., 2005).

Due to the anti-inflammatory efficacy of meloxicam in distinct tissues, we aimed to evaluate its effects in the scope of the ophthalmology, by topical and subconjunctival routes, once both of them have not yet been tested with this drug. These routes were compared to the subcutaneous route by PGE₂ and protein quantitation in the aqueous humor after experimental paracentesis in dogs. Additionally,

conjunctival histopathology was performed in order to investigate occasional interurrences related to its safety and adverse effects.

MATERIAL AND METHODS

Twenty poodles and five mongrel dogs, clinically healthy, with mean weight of 12kg, aging from 11 to 14 months were used. All animals were submitted to physical and ophthalmic (Schirmer tear test^a, biomicroscopy^b, tonometry^c, indirect ophthalmoscopy^d, and fluorescein staining^e) examination in order to exclude systemic and ophthalmic abnormalities. Once selected, dogs were housed in individual kennels, fed a dry pellet twice daily^f and water *ad libitum*, vaccinated^g, and dewormed^h.

In order to promote blood-aqueous barrier breakdown and to collect 0.2mL of primary aqueous humor (M0), all dogs underwent general anesthesia by a bolus dose of propofolⁱ (10mg kg⁻¹), and anterior chamber paracentesis of the left eye was accomplished as previously described by WARD et al. (1991). Five hours latter (M1), another paracentesis was performed to obtain 0.2mL of secondary aqueous humor.

Primary and secondary aqueous samples of each dog were transferred to Eppendorf microtubes (0.1mL in each). Both microtubes were identified and centrifugated during 5 minutes at 3500rpm; one of them was refrigerated at 5° C for total protein quantitation^j, one hour after collection, and the other one was frozen at -70° C for further prostaglandin E₂ quantitation^k.

Four groups (n=5) were formed. The group GI was treated with 0.2mg kg⁻¹ subcutaneous meloxicam^l. The group GII received the same dose of meloxicam in the dorsolateral aspect of the bulbar conjunctival of the left eye, not excising a final volume of 0.2mL. The commercial formulation was diluted in sterile water (1:1), to obtain a final solution of 0.5% to be used in a third group GIII, which received one drop on the cornea of the left eye. A control group was formed and received no treatment. Both GI and GII were treated with a single dose of carprofen by the end of M0. Literature recommends that when the topical route is instituted for management of uveitis, anti-inflammatory drugs should be instilled several times per day (COLLINS & MOORE, 1999; van der WOERDT, 2001), for this reason, only the group GIII was treated by the end of M0 and subsequently, hourly until M1.

Aqueous humor samples obtained at both moments were diluted at a proportion of 1:5 to 1:10 and kept in water bath at 37°C, during 15 minutes. Protein quantitation was performed with a commercial chemistry analyzer; results were expressed in milligram per deciliter (mg dL⁻¹).

For Prostaglandin E₂ (PGE₂) quantitation, all samples obtained at M0 and M1 were submitted to a competitive enzyme immunoassay. Samples were defrozen at room temperature, diluted at a proportion of 1:10 to 1:40 in Milli Q water. Results obtained in absorbance unities were transformed to picograms per microliters (pg mL⁻¹) in specific software^m.

Twenty four hours past M1, one drop of tetracaine/fenilefrinⁿ was topically applied and a conjunctival specimen were collected near by the site where meloxicam was injected in the animals of GII. Obeying the same criteria, a specimen of the left eye of the control animals was collected.

Biopsied eyes received ophthalmic ointment with cloranfenicol, vitamin A and aminoacids^o after the procedure, every each 8 hour, for five consecutive days. Conjunctival specimens were fixed in 10% formalin, stained with Hematoxilin–Eosin and evaluated under light microscopy.

For statistical analysis^p, conventional analyses of variance (ANOVA) and ANOVA for repeated measures with Tukey as post-hock test were used. Occasional correlation among aqueous humor level of total protein and PGE₂ were assessed by Person's correlation test with the level of significance set at $P < 0.05$. Results were expressed as mean and standard error of mean (\pm SEM).

RESULTS

Significative increased values of protein were observed in M1, in comparison to M0 ($P < 0.001$). However, after the second paracentesis (M1), values of protein did not change significantly among groups ($P = 0.75$) (Table 1). Regarding the aqueous humor concentration of prostaglandin E₂ (PGE₂), all samples evaluated at M0 measured below the limit of the assay (15.00pg mL⁻¹). Significant increased values of PGE₂ were observed in M1 ($P < 0.001$). At M1, values of PGE₂ did not change significantly among groups ($P = 0.85$) (Table 1).

Protein and PGE₂ levels correlated positively in all groups that received meloxicam: GI ($r^2 = 0.56$; $P = 0.0129$), GII ($r^2 = 0.40$; $P < 0.0001$), and in GIII ($r^2 = 0.44$; $P = 0.049$). Control group ($r^2 = 0.27$; $P = 0.123$) did not shown correlation. Under the conjunctiva of the animals of GII, histopathologic evaluation showed exudative acute inflammation and mild hemorrhage.

DISCUSSION

We aimed to study the effects of meloxicam administered by different routes after experimentally induced-uveitis in dogs, once good results were obtained with this agent in other tissues (GIULIANO, 2004) and because of its safety, when compared with other nonselective cyclooxygenase-2 NSAIDs (LUNA et al., 2007).

Even a significant difference has not being achieved, all animals treated by the subcutaneous route showed a decrease of 17% in aqueous humor protein concentration in comparison with the animals of the control group. Similar results were seen after experimental paracentesis in dogs that received meloxicam orally (GILMOUR & KENNARD, 2004).

Subconjunctival route was one of the focuses of this study, because it has advantages in establishing a greater intraocular concentration of drug that is possible only when frequent topical applications are used, in addition to its reduced costs (GIULIANO, 2004). The reduction in protein levels was of only 2.70% compared to the control group, similar results were reported when flunixin meglumine was used subconjunctivally in dogs (GALERA, 2002).

Subconjunctival route showed the lesser efficacy to inhibit the protein influx into the anterior chamber when compared with the other treated groups. A previous study reported that higher intraocular concentrations in the anterior segment of the eye were achieved by this route in comparison to the systemic route (GHATE et al., 2007). It may be admitted, that due to the interval adopted between each aqueoucentesis,

Table 1 - Mean (\pm SEM) values of aqueous humor total protein (mg dL⁻¹), and prostaglandin E₂ (pg mL⁻¹) in all studied groups, at moments 0 and 1.

Total Protein	GI	II	GIII	Control	P Value*
M0	18.22 \pm 5.3	14.61 \pm 1.65	17.18 \pm 4.08	10.25 \pm 2.35	1.00
M1	268.98 \pm 78.52	305.83 \pm 63.14	261.92 \pm 60.60	314.32 \pm 62.06	0.79
PGE ₂					
M0	15.00	15.00	15.00	15.00	1.00
M1	1000.00	999.69 \pm 0.30	749.73 \pm 126.02	814.05 \pm 185.95	0.85

*Tukey's test. GI: subcutaneous route, II: subconjunctival route, GIII: topical route.

desirable indexes of the drug could not be able to reach the anterior chamber, like reported by GALERA (2002).

Pharmacokinetic data of subconjunctival meloxicam administration were not established yet. Time between drug administration and the second aqueoucentesis was conceived in accord with pharmacokinetic parameters when the drug is used by the subcutaneous route, particularly when the higher plasmatic peak is achieved, which occurs in an average of two and half hours followed administration (BUSCH et al., 1998). When administered by the subconjunctival route, drugs reach the anterior chamber and the vitreous chamber, preferably at equatorial region of the eye, where the scleral thickness is more tenuous (GILGER et al., 2005). Furthermore, hematogenous absorption occurs by subconjunctival vessels, contributing that fractions of the drug reach the systemic circulation and penetrate the eye (GHATE et al., 2007). Studies regarding the pharmacokinetic of drugs in the aqueous humor are quite complexes, once repeated collections are able to modify the aqueous composition, which results in qualitative alterations of this fluid (ROZE et al., 1996).

GHATE et al. (2007) reported that increased volumes of sodium fluorescein delivered to the eye by different periocular routes have a larger role in transcleral drug delivering than this concentration itself; thus, the inefficacy of carprofen in blocking the anterior uveal tract inflammation may also be explained by the low dose used in this study. Moreover, the high viscosity of the agent hindered that higher volumes could be injected into the subconjunctival space.

Topical route is preferable for the management of uveitis, once it is simple to use and provides desirable intraocular drug concentration. In addition, this route is advantageous once lesser adverse effects are elicited (HOLMBERG & MAGGS, 2004; GIULIANO, 2004). The severity of inflammation dictates the frequency in which anti-inflammatory drugs should be instilled (HOLMBERG & MAGGS, 2004; GIULIANO, 2004). Factors affecting bioavailability of NSAIDs by the topical route include corneal penetrability, corneal stromal metabolism, and corneal stromal protein binding (WARD, 1996). Particle size may be the most important formulation in determining the bioavailability of the active molecule suspension (ROBERTS & NELSON, 2007).

Topical route was tested herein considering that NSAIDs in general, show similar or even a stronger effect than corticosteroids when used by this route (KROHNE et al., 1998). Nonsteroidal anti-inflammatory drugs suppress the protein influx to aqueous humor, after one hour and a half, whereas corticosteroids may

need six hours after administration to show action by inhibitory effects on expression of the messenger RNA-encoding cyclooxygenases-related protein (HAYASAKA et al., 2003; ABE et al., 2004). The reduction of only 27% in protein levels, contrasts the observations of a previous study, which proved that topical flurbiprofen, diclofenac, and suprofen were effective at preventing blood-aqueous barrier disruption after paracentesis in dogs (WARD, 1996).

Once prostaglandins, notably prostaglandin E_2 , act as the major chemical mediator involved in the pathogenesis of anterior uveitis, we aimed to study it. At the first moment, prostaglandin E_2 concentration was below the detection limit of the commercial assay (15.00pg mL^{-1}), in accordance with GILMOUR & LEHENBAUER (2006). At the second moment, the average of prostaglandin E_2 found in the control group was 827.76pg mL^{-1} , differing from GILMOUR and LEHENBAUER (2006) findings, in which dogs that composed the control group achieved an average of 194.17pg mL^{-1} of prostaglandin E_2 in the aqueous. Furthermore, in contrast to our results, dogs treated with oral tepoxalin (NSAID) showed significant reduced values in comparison with controls (GILMOUR & LEHENBAUER, 2006).

Despite GILMOUR & LEHENBAUER (2006) have used the same methods that we did, for both induction and quantification of the uveitis, that study evaluated prostaglandin E_2 levels one hour after the first aqueoucentesis, differently of the five hours adopted in the present study. Considering that the uveal tract has low amounts of the dehydrogenase-15 PG, which is responsible for the inactivation of prostaglandin E_2 , and also because its activity is decreased in cases of uveitis may explain the exacerbated concentration of prostaglandin E_2 at the second moment (COLLINS & MOORE, 1999). In addition, the NSAID (tepoxalin) used in that study was administered one hour before paracentesis (GILMOUR & LEHENBAUER, 2006). HAYASAKA et al. (2003) and ABE et al. (2004) demonstrated that topical or intravenous administration of nonsteroidal anti-inflammatory drugs are able to suppress the protein influx to aqueous humor, only when used one hour and a half before the blood-aqueous barrier breakdown.

Our results also differ from those of MILLICHAMP et al. (1991), which reported that flunixin melgumine was capable to inhibit prostaglandin E_2 synthesis in the aqueous humor of dogs, followed one hour of its intravenous administration. However, one may consider that the authors used indirect immunofluorescence to detect prostaglandin E_2 in the aqueous humor (MILLICHAMP et al., 1991).

A positive correlation was found only for all the animals treated with meloxicam. Such findings were not observed when dogs received tepoxalin orally (GILMOUR & LEHENBAUER, 2006).

In the animals that received the agent by the subconjunctival route, acute exudative inflammation and hemorrhage could be seen, which could be attributed to trauma elicited by the injection. Subconjunctival plaques were not noted, as once referred by GALERA (2002) in a study where flunixin meglumine was evaluated by the same route.

CONCLUSION

Despite meloxicam was proved to be safe by any of the tested routes, the agent was unable to inhibit the synthesis of PGE₂ and the protein influx to the anterior chamber, when administered after paracentesis induced-uveitis in dogs.

ETHICS COMMITTEE ON ANIMAL EXPERIMENTATION

This study was approved by the Ethics Committee on Animal Experimentation of the Faculty of Agricultural and Veterinary Sciences (FCAV) of Sao Paulo State University (UNESP), Jaboticabal, Sao Paulo, Brazil (Protocol nº 011964-06), and followed the ethical norms of the Association for Research in Vision and Ophthalmology ARVO (National Institutes of Health, Publications no. 85-23, revised 1985).

SOURCES OF ACQUISITION

a-Teste de Schirmer®, Ophthalmos – São Paulo – SP
b-Portable slit lamp SL 14®, Kowa – Japan
c-Tonopen XL®, Mentor O&O – Norwell, MA, USA
d-Oftalmoscópio binocular indireto OHC®, Eye Tec – São Carlos – SP
e-Fluoresceína Strips®, Ophthalmos – São Paulo – SP
f-Special Croc®, Royal Canin AS – Descalvado – SP
g-Duramune Max®, FortDoge Saúde animal – Campinas – SP
h-Ivermectina 1%® Ourofino, Ribeirão Preto - SP
i-Diprivan®, Cristália, São Carlos, São Paulo
j-Sensiprot®, Labtest – Lagoa Santa, MG
k-Prostaglandin E₂ EIA KIT (monoclonal)®, Cayman chemical – Ann Arbor, MI, EUA
l-Movatec®, Boehringer Ingelheim – Itapeverica da Serra – SP
m-www.caymanchem.com/analysis®, Cayman chemical – Ann Arbor, MI, EUA
n-Anestésico®, Allergan– Guarulhos, São Paulo
o-Epitezan®, Allergan– Guarulhos, São Paulo
p-SigmaStat 3.0®, Systat Software inc - San Jose, CA, USA

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