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Firocoxib on aqueous humor prostaglandin E_2 levels for controlling experimentally-induced breakdown of blood-aqueous barrier in healthy and *Toxoplasma gondii*-seropositive cats

Efeitos do firocoxib sobre os níveis de prostaglandina E_2 no humor aquoso de gatos saudáveis e com sorologia positiva para toxoplasmose mediante quebra da barreira hematoaquosa experimentalmente induzida

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ABSTRACT

*This study aimed to evaluate the effects of firocoxib for controlling experimentally-induced breakdown of the blood-aqueous barrier in healthy and **Toxoplasma gondii**-seropositive cats. Thirty two cats with no ocular abnormalities were used. Groups (n=8/each) were formed with healthy cats that received 5mg g^{-1} of oral firocoxib (FH) or no treatment (CH) on day 0; seropositive cats for anti-**T. gondii** specific immunoglobulin G (IgG) were grouped (n=8/each) and treated in a similar fashion (FT and CT). On day 1, cats of all groups received the same treatment protocol, and 1h later, aqueocentesis was performed under general anesthesia (M0). Following 1h, the same procedure was repeated (M1). Quantitation of aqueous humor total protein and prostaglandin E_2 (PGE_2) were determined. Aqueous samples of seropositive cats were tested for anti-**T. gondii** specific IgG. In M0, aqueous samples of CT showed a significantly higher concentration of PGE_2 in comparison with other groups ($P<0.05$). In all groups, PGE_2 concentration increased significantly from M0 to M1 ($P=0.001$). PGE_2 values did not change significantly between groups in M1 ($P=0.17$). Anti-**T. gondii** specific IgG were reported only in samples of M1, and aqueous titers did not change significantly between FT and CT ($P=0.11$). Although we have observed that aqueous humor PGE_2 levels were significantly higher in cats of CT group during M0, such increase was not able to break the blood-aqueous barrier and cause anterior uveitis. Firocoxib did not prevent intraocular inflammation after aqueocentesis, in healthy and toxoplasmosis-seropositive cats.*

Key words: *aqueous humor, intraocular inflammation, NSADs, toxoplasmosis*.

RESUMO

*Objetivou-se avaliar a eficácia do firocoxib no controle da quebra da barreira hematoaquosa experimentalmente induzida em gatos saudáveis e com sorologia positiva para toxoplasmose. Para tanto, utilizaram-se trinta e dois gatos sem alterações oculares, alocados em grupos (n=8/cada) compostos por gatos saudáveis que receberam tratamento prévio com 5mg g^{-1} de firocoxib oral (HF) ou sem nenhum tratamento (CH) no dia 0, e por gatos com sorologia positiva para toxoplasmose tratados de maneira similar (FT e CT). No dia 1, os gatos de todos os grupos receberam o mesmo protocolo de tratamento do dia anterior e, 1h depois, foram submetidos à paracentese da câmara anterior sob anestesia geral (M0). Após 1h, realizou-se nova paracentese (M1). Mediante a colheita de humor aquoso (M0 e M1), quantificaram-se os valores de proteína total e prostaglandina E_2 (PGE_2) das amostras. As amostras dos gatos com sorologia positiva para toxoplasmose foram também testadas para anticorpos anti-**T. gondii** IgG específicos. Em M0, as amostras de humor aquoso de CT apresentaram concentração de PGE_2 significativamente superior aos demais grupos ($P<0,05$). Em todos os grupos, a concentração de PGE_2 aumentou significativamente de M0 para M1 ($P=0,001$), no entanto, não houve diferença significativa entre os grupos em M1 ($P=0,17$). Anticorpos anti-**T. gondii** IgG específicos foram encontrados somente em amostras de M1, e os*

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títulos não diferiram significativamente entre FT e CT (P=0,11). Valores de PGE_2 significativamente superiores no CT durante M0 não foram capazes de induzir a quebra da barreira hematoaquosa e causar uveíte anterior nos gatos deste estudo. O firocoxib, por sua vez, não foi capaz de prevenir a quebra da barreira hematoaquosa após realização de paracente na câmara anterior em gatos saudáveis e com sorologia positiva para toxoplasmose.

Palavras-chave: *humor aquoso, inflamação intraocular, AINEs, toxoplasmose*.

INTRODUCTION

Immune-mediated and neoplastic diseases, intraocular surgeries, fungal, parasitic, bacterial, and viral infections may cause breakdown of the blood-aqueous barrier (BAB). Such an event leads to the exudation of plasma proteins and cells into the anterior chamber of the eye, promoting aqueous flare, in association with decreased intraocular pressure and miosis (GELATT & WILKIE, 2011). Prostaglandins (PG) are the main inflammatory mediators involved in the breakdown of the BAB (GELATT & WILKIE, 2011).

Topical corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) are used in order to control ocular inflammation, minimize ocular sequelae and preserve vision (COLITZ, 2005). However, adjunct systemic anti-inflammatory therapy is required in cases of posterior or severe anterior uveitits (GELATT & WILKIE, 2011). In this regard, systemic NSAIDs may be indicated in cases of infectious uveitis or in patients with diabetes ***mellitus*** (COLITZ, 2005). Cyclooxygenase-2 (COX) selective NSAIDs are able to improve signs of inflammation and pain, minimizing the occurrence of adverse effects, such as gastrointestinal irritation, glomerular injury, and inhibition of platelet aggregation, usually associated to the suppression of COX-1 enzyme (MONTEIRO-STEAGALL et al., 2013). In cats, firocoxib guarantees the inhibition of 80 to 90% of COX-2, and less than 20% of COX-1 (MCCANN et al., 2005). Although not approved for cats, it has been showed in this species that the oral administration of 1mg kg^{-1} of firocoxib for 8 consecutive days did not cause gastritis and had the same potential to inhibit PGE_2 synthesis as meloxicam, another COX-2 selective NSAID (GOODMAN et al., 2010).

In dogs, several studies have been conducted in order to evaluate the efficaciousness of systemic administered COX-2 selective NSAIDs for controlling the breakdown of the BAB (GILMOUR & LEHENBAUER, 2009; RIBEIRO et al., 2009; PINARD et al., 2011). However, only one study has described the effects of oral meloxicam in cats with experimentally-induced uveitis (RANKIN et al., 2013).

Toxoplasmosis is caused by the coccidial protozoa, ***Toxoplasma gondii*** (***T. gondii***), in which the feline is the definitive host. In cats, this agent may cause uni or bilateral uveitis in otherwise systemically asymptomatic immune-competent individuals (MEUNIER et al., 2006). There are no reports of aqueous humor PGE_2 quantitation in healthy and in ***T. gondii***-seropositive cats. Considering that the prevalence rates of ***T. gondii*** in cats from Brazil range from 5.6 to 87.3% (BASTOS et al., 2014), and that the specific anti-***T. gondii*** IgG titers remain high for 2 years or longer in the cat population (DAVIDSON & ENGLISH, 1998), it seems to be reasonable to evaluate these effects of firocoxib for controlling experimentally-induced anterior uveitis in healthy and in ***T. gondii***-seropositive cats.

MATERIALS AND METHODS

Thirty two male domestic shorthair cats were enrolled in the study. Only cats with no abnormalities detected on cardiac and respiratory rate, capillary refill time, temperature, skin turgor, Schirmer's tear test, slit lamp biomicroscopy, intraocular pressure, ophthalmoscopy, fluorescein test, haematological, biochemical tests (alanine aminotransferase, albumin, and blood urea nitrogen), and tested negative for Feline Immunodeficiency and Leukemia Virus were included in the study. Seropositive and seronegative cats for ***T. gondii*** were grouped separately. Selected animals were exposed to 12 hours of light/dark cycle, were fed with dry cat food twice daily, and provided with water ***ad libitum***.

Four separate groups (n=8) were formed. Firocoxib-treated healthy (FH) and firocoxib-treated toxoplasmosis (FT) groups were composed of seronegative and seropositive cats, respectively, that received 5mg g^{-1} of oral firocoxib[a] on days 0 (8 a.m.) and 1 (8 a.m. of the next day, 1 hour before the aqueocentesis). The groups control healthy (CH) and control toxoplasmosis (CT) were composed of seronegative and seropositive cats, respectively, and received no previous treatment. Seropositive and seronegative cats were picked at random to be included into control or firocoxib-treatment groups.

Food was withheld for 12 hours before anesthesia, but cats had free access to water. General anesthesia was induced with an intravenous injection (10mg g^{-1} as needed) of propofol[b] and was maintained with isoflurane[c]. Cats were positioned

in left lateral recumbency and the periocular skin and the conjunctival sac were gently washed with povidone-iodine diluted in saline (1:50). In order to disrupt the BAB, anterior chamber paracentesis of the right eye was performed and 0.2mL of primary aqueous humor (M0) was slowly aspirated. One hour later (M1), the same procedure was repeated to obtain 0.2mL of secondary aqueous humor. Aqueous samples of each cat were identified and frozen at -80ºC for further prostaglandin E_2 and total protein quantitation. Aqueous samples of seropositive cats were also tested for anti-***T. gondii*** specific IgG.

At the end of M1, all cats were castrated, and the eyes received one drop of the following medications: 1% atropine[d] (q 12h), 0.3% tobramycin[e] (q 6h), and 1% prednisolone[f] (q 6h), for approximately 3 days or until complete remission of aqueous flare. In addition, animals were treated with subcutaneous meloxicam[g] (0,1mg g^{-1} q 24h) for 3 consecutive days. Such protocols were adopted to ensure analgesia and prevent sequelae caused by the experimental uveitis induction (COLITZ, 2005), regardless of the results of the tested drug.

Enzyme-linked immunoassay[h] was performed in microplates to determine aqueous humor prostaglandin E_2 concentration according to the manufacturers' protocols. All aqueous samples were thawed at room temperature and measured in duplicate with no dilution. The absorbance was read at 420nm, and values were converted to picograms per microliters (pg mL^{-1}). Mean highest calculated standard concentration for the assay plates was 1,032pg mL^{-1}; therefore, the upper limit for the PGE_2 concentration in samples was truncated at 1,000pg mL^{-1} for statistical analysis of data.

Aqueous humor total protein concentration was determined via commercial colorimetric assay kit[i], also in accordance to the manufacturers' protocols. The absorbance was read at 600nm and values expressed in milligrams per deciliters (mg dL^{-1}).

Serum and aqueous humor anti-***T. gondii*** specific IgG were assessed by means of Indirect Fluorescence Antibody Test (IFAT) as previously described by CAMARGO (1964) using tachyzoites of RH strain of ***T. gondii*** propagated in VERO cell culture. The serologic cut-off titer was established at ≥1:64.

Shapiro-Wilk test was used to assess data normality. For each group, Wilcoxon´s and Student´s paired T tests were used to compare values of aqueous humor PGE_2 and total protein, respectively, from M0 to M1. Comparisions of PGE_2 and total protein values among groups after the first paracentecis (M0), were assessed by 1-ANOVA, followed by Bonferroni´s test. After the second paracentesis (M1), the Kruskal-Wallis test was used to check for differences of PGE_2 values among groups; whereas 1-ANOVA was used to compare total protein values among groups. Aqueous humor titers of anti-***T. gondii*** specific IgG obtained after the second paracentesis (M1), in groups CT and FT were compared by Man Whitney test. In all ocasions, differences were considered significant when $P<0.05$ (Prism 4.0-GraphPad Software inc, California, USA).

RESULTS

Serum anti-***T. gondii*** IgG titers in selected cats ranged from 1:64 to 1:8192 (median 1:1493). The mean (±SEM) of PGE_2 aqueous humor levels (pg mL^{-1}) obtained during M0 was 6.35±0.97 (CH), 7.41±1.64 (FH), 29.20±4.99 (CT), and 14.89±5.24 (FT). In M0, aqueous samples of CT group showed a significantly higher concentration of PGE_2 in comparison with other groups ($P<0.05$). Median (range) PGE_2 aqueous humor levels (pg mL^{-1}) obtained during M1 was 52.95 (4.50-1,000.00) (CH), 63.80 (13.40-375.80) (FH), 241.20 (47.80-1,000.00) (CT), and 304.40 (4.10-1,000.00) (FT). In all groups, PGE_2 concentration increased significantly from M0 to M1 ($P<0.05$). However, PGE_2 levels did not change significantly between groups in M1 ($P=0.17$).

Mean (±SEM) total protein aqueous humor levels (mg mL^{-1}) obtained during M0 was 29.81±3.09 (CH), 42.31±2.03 (FH), 31.25±3.38 (CT), and 45.84±2.60 (FT). In M0, aqueous samples of HF and TF groups showed a significantly higher concentration of total protein in comparison with HC and TC groups ($P<0.05$). Mean (±SEM) total protein aqueous humor levels (mg mL^{-1}) obtained during M1 were 115.10±7.97 (CH), 117.20±3.75 (FH), 129.30±4.04 (CT), and 126.6±10.76 (FT). In all groups, total protein concentration increased significantly from M0 to M1 ($P<0.05$). However, total protein levels did not change significantly between groups in M1 ($P=0.44$).

Aqueous samples of 7 cats of CT and 5 of FT groups tested positive for anti-***T. gondii*** IgG. Aqueous titers ranged from 1:256 to 1:8,192 in CT group (median 1:2,048), and from 1:128 to 1:2,048 (median 1:256) in FT; titers did not change significantly between FT and CT ($P=0.10$).

DISCUSSION

This study showed that baseline aqueous humor PGE_2 levels of healthy cats are similar to dogs

(GILMOUR & LEHENBAUER, 2009; RIBEIRO et al., 2009; PINARD et al., 2011), and lower than in horses (HILTON et al., 2011). However, cats in the CT group showed significantly higher baseline levels of aqueous PGE_2 than the other groups. Such an increase, however, of approximately 23pg mL^{-1}, was not enough to induce disruption of BAB, as confirmed by the total protein aqueous humor levels assessed during the first aqueocentesis.

It has been reported that ***T. gondii***-infecting skeletal muscle cells increases the synthesis of lipids of the cell, contributing to the growth and maturation of the parasitophorous vacuole (GOMES et al., 2014). Such an increase in the lipid levels within the vacuoles may contribute to the heightened eicosanoid production during ***T. gondii*** infection (GOMES et al., 2014). Thus, one should consider that the higher aqueous humor of PGE_2 levels observed in cats of CT group, may have arose as a result of fatty degradation acids of the host cell used by the parasite as an energy source. Even considering that the seropositive cats used in this experiment were asymptomatic, it is possible that cellular necrosis of peripheral ocular tissues, resulted from intracellular growth of ***T. gondii***, may have not been noticed during slit lamp and ophthalmoscopy examination.

Results showed that firocoxib was unable to inhibit the breakdown of the BAB after aqueocentesis in healthy and seropositive cats, as confirmed by the increased concentration of aqueous humor PGE_2 and total protein obtained during M1 in all groups studied. Fluorophotometry was used to evaluate the BAB in healthy cats; authors described that cats treated with oral meloxicam for 2 days before aqueocentesis-induced breakdown of the BAB, showed decreased anterior chamber fluorescein concentration and decreased intraocular inflammation was noticed only 48 hours after aqueocentesis (RANKIN et al., 2013). In a similar study conducted in dogs, PINARD et al. (2011) also reported that a 2 day treatment with oral carprofen, administrated before the breakdown of the BAB by aqueocentesis was necessary to control intraocular inflammation.

It has been reported in cats, that firocoxib resulted in significantly lower plasma PGE_2 levels following 3 days of oral administration (GOODMAN et al., 2010). Nonetheless, COX et al. (2013) observed that horses treated with triple the dose of firocoxib, showed at 24 hours after the loading dose, a steady state concentration of the drug, which was similar when the drug was administered for 7 consecutive days. In this study, a triple dose of oral firocoxib was not capable to inhibit the breakdown of the BAB. Likewise, firocoxib did not control intraocular inflammation (PGE_2 concentration), in horses treated for 7 consecutive days before the disruption of BAB by aqueocentesis (HILTON et al., 2011).

It has been described in cats that peak plasma concentration of firocoxib is reached following 4 hours of oral administration (MCCANN et al., 2005). Ineffectiveness of firocoxib for controlling the breakdown of BAB seen herein may be attributed to the 1 hour interval used in our protocols, between the first and second aqueocentesis. The reason why cats were treated for one day before and one hour before the first aqueocentesis, followed by a short period of time to perform the second aqueocentesis, was to mimic the routine protocols that are usually adopted by many veterinary ophthalmologists, regarding systemically administered NSADs, before cataract surgery in dogs (MCLEAN et al., 2012).

Aqueous humor PGE_2 levels of cats of FT group were significantly lower in comparison to aqueous humor PGE_2 levels of cats of CT group after the first aqueocentesis. According to Hilton et al. (2011), the lipophilic nature of the drug results in greater distribution and tissue binding which may explain the lower PGE_2 levels seen in cats of FT group during M0.

Aqueous humor protein concentrations collected in M0 and M1 are in accordance to what has previously been reported in another study (RANKIN et al., 2002). It was also observed that aqueous humor total protein concentration was significantly higher in FH and FT groups. This may suggest that the protein influx into the aqueous humor may be attributed to the high affinity of firocoxib to albumin (BOOTHE, 1989). However, firocoxib did not prevent the disruption of the BAB or the increase of aqueous humor total protein levels in treatment-groups. Conversely, immunoglobulins are high molecular weight proteins that usually enter the eye through breaches of the BAB or when infections are present (NIU et al., 2011). It has been demonstrated that aqueous humor anti-***T. gondii*** specific IgG is detected in experimentally infected cats, following 20 days of ***T. gondii*** inoculation (LAPPIN et al., 1997). Another paper has shown that ***T. gondii***-seropositive asymptomatic cats do not present aqueous humor titers for the parasite (LAPPIN, 2000); the same has been observed in cats of CT and FT groups of this study. GARCIA et al. (2007) observed lower aqueous humor titers for anti-***T. gondii*** IgG in comparison to serum titers in experimentally infected pigs. Similar findings have been reported in cats (MEUNIER et al., 2006). In this research; however, aqueous humor

titers for anti-***T. gondii*** could only be detected during M1, but aqueous titers were similar or even higher than serum titers of cats in the CT group.

CONCLUSION

From observations of our study, it can be concluded that although aqueous humor PGE_2 levels were significantly higher in cats in the CT group during M0, the increase was unable to break the BAB. Firocoxib did not prevent intraocular inflammation after aqueocentesis, in healthy or toxoplasmosis-seropositive cats.

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ETHICS COMMITEE

This study was approved by the institutional Committee for Ethics in the Use of Animals (Universidade Federal de Mato Grosso – UFMT) on Jun 27, 2013 (protocol 23108.021796/13-9).

SOURCES OF ACQUISITION

a - Previcox® 57mg, Merial, Brazil.
b - Propovan® 10mg mL^{-1}, Cristália, Brazil.
c - Isoforine® 100mL, Cristália, Brazil.
d - Atropina 1%®, Allergan, Brazil.
e - Tobramicina 0,3%®, Germed, Brazil.
f - Pred Fort®, Allergan, Brazil.
g - Maxicam® 0,2%, Ouro Fino, Brazil.
h - Prostaglandin E_2 EIA KIT monoclonal®, Cayman chemical – Ann Arbor, MI, EUA.
i - Proteinúria – PP®, Analisa, Brazil.

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