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BASIC SCIENCE

Pharmacokinetics and efficacy of intraocular flurbiprofen

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Abstract
Purpose Intravitreal delivery of non-steroidal anti-inflammatory drugs could be an effective way to treat macular edema caused by posterior segment inflammation. In this study, we evaluated the intravitreal bioavailability and anti-inflammatory efficacy of flurbiprofen in rabbit eyes.
Methods For pharmacokinetics, 0.1 ml of 7.66 mg/ml flurbiprofen solution was injected intravitreally and vitreous drug levels were analyzed at specific time points using LC-MS technique. For efficacy, 100 ng lipopolysaccharide of E.coli was injected intravitreally in rabbits to induce inflammation. The animals were separated in three groups and received intraocular flurbiprofen, dexamethasone and PBS to serve as control. Complete ocular examination and total cell count in aqueous fluid were determined to evaluate the extent of inflammation. Eyes were then enucleated for histopathology analysis. The efficacy in the uveitis model was determined by clinical signs of inflammation, total leukocyte count and histology findings.
Results No adverse events were observed during pharmacokinetic assessment. No signs of inflammation, hemorrhage or retina detachment were detected. The recovery of flurbiprofen from vitreous samples was 92.6%. The half-life of flurbiprofen was estimated to be 1.92 h with an elimination constant rate (K) of 0.36. Treatment with intraocular injections of flurbiprofen and dexamethasone significantly reduced total leukocyte count in a manner comparable to dexamethasone [reduction of 96.84% ($p < 0.05$) and 97.44% ($p < 0.05$), respectively]. Histologic studies demonstrated significantly less signs of ocular inflammation after flurbiprofen injection compared to control eyes.
Conclusions Flurbiprofen is effective in suppressing inflammation in this experimental uveitis model. In our experimental setting, intravitreal flurbiprofen seem to have a therapeutic result comparable to dexamethasone. However, the half-life of the drug remains short, necessitating further research to prolong its presence in the vitreous cavity.

Keywords NSAIDs · Flurbiprofen · Intravitreal delivery · Inflammation

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of cyclooxygenase (COX) enzymes and thereby reduce the biosynthesis of proinflammatory prostaglandins (PGs) from arachidonic acid [1]. Intraocular PGs disrupt the blood ocular barrier, increase vasodilation and facilitate leucocyte migration. NSAIDs are used nowadays as eye drops to treat inflammation of ophthalmic surface as well as to reduce macula edema after cataract surgery. However, topical or oral application of NSAIDs does not provide sufficient therapeutic levels to the posterior ocular segment. On the other hand, intraocular administration could impart significantly higher levels to the retina while minimizing systemic adverse events.

Corticosteroids are being used intravitreally as anti-inflammatory agents for the treatment of macula edema. However, corticosteroids are associated with side effects such as cataract formation and elevation of intraocular pressure [2,

3]. Consequently, NSAIDs could be an alternative for the treatment of inflammation of the posterior segment of the eye.

Flurbiprofen (FLB) is a potent non-steroidal agent, which inhibits COX-1 and COX-2 enzymes. Similar in structure to ibuprofen, naproxen, fenoprofen and ketoprofen, this propionic acid derivative possesses analgesic, anti-inflammatory and anti-pyretic properties. FLB is used systemically for symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and topically for the treatment of ocular surface inflammation and after cataract surgery [4]. FLB was found to be safe and nontoxic up to a dose of 0.1 ml after intravitreal administration [5].

In this study, we evaluated firstly the pharmacokinetics of FLB after intravitreal injection and secondly the anti-inflammatory efficacy of intraocular FLB in an animal model of uveitis.

Materials and methods

Animals

Pigmented rabbits were used in our experiments due to the fact that human eyes are also pigmented and the bioavailability of the drug can be influenced by eye pigmentation [6]. All the experimental procedures followed the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and the institutional guidelines. The rabbits were housed in separated cages and were maintained in a controlled environment: 12-h on/off light cycle at 25 °C. Twenty nine (29) adult pigmented rabbits, weighting from 2 to 3 Kg each, were included in the study. Fifteen (15) rabbits were used to evaluate vitreous bioavailability and fourteen (14) rabbits were used in the uveitis model.

Animal experimental procedure

Pharmacokinetics

FLB (COOPER Pharmaceuticals, Greece) was acquired in powder form and dissolved in phosphate-buffered saline (PBS; Sigma-Aldrich, St. Louis, MO, USA). A concentration of 7.66 mg/ml was prepared for intravitreal administration. According to Morales and coworkers, doses up to 1 mg of FLB do not cause retinal toxicity in rabbit eyes [7].

Animals were anesthetized by an intramuscular injection of a mixture containing ketamine hydrochloride (50 mg/kg) and xylazine (5 mg/kg) solution. Additional topical anesthesia to the eyes was applied (one drop of sodium chloride proxymetacain, Alcaine, ALCON Lab, Hellas AEBE). 5% of povidone-iodine solution was applied and a 30-gauge needle on a 1-ml tuberculin syringe was inserted 2 mm posterior to the limbus superiorly (12th hour). The drug was inserted slowly to the mid-vitreous cavity. In order to avoid drug reflux, the syringe remained in the vitreal cavity for 10 sec and then was retrieved slowly.

Examinations

Rabbits underwent slit-lamp biomicroscopy and indirect ophthalmoscopy. Animals were examined prior to any intervention and in a frequent base: at each time point during pharmacokinetic assessment and daily when evaluating the anti-inflammatory effects.

Evaluation of vitreous clearance

For pharmacokinetics, rabbit eyes were injected with 0.766 mg of FLB (volume of 0.1 ml, intravitreally). The animals were euthanized at specific time points; 0, 1, 3, 12, 24 h [8]. Three eyes per time point were enucleated and placed at -80 °C. The frozen vitreous was eviscerated whole from all eyes (1.1 ± 0.2 ml), and the samples were mechanically homogenized for 2 min.

Working solution and samples

FLB (99.5%) was purchased by COOPER Pharmaceuticals, Greece. Methanol [liquid chromatography-mass spectrometry (LC-MS) grade] was obtained from Fluka (St. Louis, MO, USA) while formic acid (>98%) was purchased from Riedel-de Haen (Seelze, Germany). Ultrapure water was produced by a Direct-Q 3UV water purification system (Merck, Germany). Working solutions of FLB were prepared in a concentration range of 0, 0.5, 1, 2.5 and 5 μg/ml by further dilutions of its stock solution (100 μg/ml) in water and stored at -20°C.

Chromatographic analysis

An LC-MS system (Shimadzu) was used for the analysis of FLB: the system consisted of a binary pump, a vacuum degasser, an autosampler and a diode array detector (DAD). A solvent mixture of 0.1% formic acid in water and methanol (15–85% *v*/v) was selected for the separation of FLP by a Discovery C18 HPLC column (250 × 4.6 mm, 5 μm) held at 30°C, with a flow rate of 0.6 mL/min. FLB's retention time was 8.1 min.

Both a DAD and a mass spectrometer (APCI interface) were used to detect the FLB in vitreous samples. The interface, curved desolvation line (CDL) and heat block temperatures were 400°C, 200°C and 200°C, respectively. The detector voltage was 1.5 kV, the nebulizing gas flow was 2.5 L/min and the drying gas was set at 0.02 MPa. The WL max of FLB was set at 245 nm while the m/z ions 199.1 and 243.15 were

used for the determination and quantification of FLB (the ion used for quantification is in bold).

Extraction of FLB from vitreous

An amount of 1.1 ± 0.2 ml of vitreous was collected at each time point, sonicated for 2 min in an ultra sonic bath and centrifuged at 4000 rpm for 5 min; 10 μl were injected into the LC-MS system with no further extraction steps. The method was linear, in that $r^2 = 0.9980$ for MS and 0.9999 for DAD. The mean recovery of FLB was calculated at 92.6 ± 2.1% while the limits of determination and quantification were 0.014 and 0.046 μg/ml, respectively.

Rabbit model of uveitis

A rabbit uveitis protocol was set in our laboratories based on other studies [9–11]. To validate the uveitis model, two doses of intravitreal endotoxin of *E. coli* were prepared to find the appropriate model for applying the drug solutions. Doses of 100 ng and 250 ng (volume of 0.1 ml intravitreally) were set for intravitreal administration. Rabbits were first anesthetized and one drop of proxymetacaine hydrochloride phenylephrine, tropicamide and cyclopentolate was applied three times for iris dilation. The ocular surface was prepared using drops of proxymetacaine hydrochloride and povidone iodine.

A total of eight rabbits were injected in both eyes with a low dose (4 rabbits) and a high dose of endotoxin (4 rabbits) using a 30-gauge needle 2 mm posterior to the limbus (12th hour). Animals were followed using slit-lamp microscopy and indirect ophthalmoscopy. Aqueous samples were obtained by anterior chamber paracentesis using a 30-gauge needle. Total leucocyte count was measured with hemocytometer at specific time points: 0, 8, 12, 18, 24, 36, 42 and 48 h. Both groups developed inflammatory reaction after the injection. However, the reaction in the group that received 250 ng was very intense, making interpretation difficult. Based on these findings, the 100-ng endotoxin dose was selected for the rest of the experiment.

Ten rabbits were used for this study. The animals were injected with 100 ng of endotoxin in the vitreous cavity of both eyes. In 5 animals, 1 eye received 2 consecutive intraocular doses of FLB (14 mg/ml; maximum dilution of FLB) at time points 12 and 18 h after intravitreal endotoxin, while their other eye received 2 consecutive intraocular doses of PBS at the same time points (12 and 18 h) and served as controls. In the other 5 animals, 1 eye received two consecutive intraocular doses of dexamethasone (4 mg/ml) at 12 and 18 h and served also as controls, while their other eye was left untreated and was not included in the evaluation. At time points 24 h and 48 h, aqueous humor was removed (approximately 200 μl) from the anterior chamber using a 30-gauge needle from the eyes of the three evaluated groups (FBP, PBS and dexamethasone) and total cell count was immediately performed. Clinical examination including slit-lamp biomicroscopy, indirect fundoscopy and intraocular pressure (iCare PRO tonometer) measurement were performed in all evaluated eyes.

Histology

The rabbits, used to determine the efficacy in the uveitis model, were euthanized and their eyes were prepared for histology. Eyes were enucleated and prefixed in cold glutaraldehyde 2.5% in 0.1 M cacodylate buffer (pH 7.4). After short prefixation, sections of the posterior segment were prepared and placed in the same fresh fixative. Tissue samples were post-fixed in osmium tetroxide in 0.1 M cacodylate buffer (pH 7.4) for 1 h at 4 °C, dehydrated in a series of alcohols and propylene oxide and then imbedded in epoxy resin. Light microscopy was performed on 1 to 3-μm sections and stained with rapid trichrome 5%. The examination was prepared with a binocular Diaplan microscope.

Results

Clinical findings: pharmacokinetics

All animals had no clinical findings when examined prior to any intervention. Most of them had pigmentation in the periphery of the fundus as a physiological fundus sign. Biomicroscopical evaluation during the follow-up revealed no sign of ocular toxicity. Specifically, no signs of corneal opacities and cataract formation had occurred. None of the animals had any sign of inflammation caused by the injection procedure. Indirect ophthalmoscopy demonstrated no signs of retinal detachment, hemorrhages or endophthalmitis during the follow-up of the pharmacokinetics experiment.

Bioavailability of FLB

Table 1 shows the intravitreal concentrations and Table 2 shows the pharmacokinetic parameters of FLB. The half-life of FLB solution was estimated to be 1.92 h with an elimination constant rate (K) of 0.36 (Fig. 1).

Efficacy in the uveitis model

Intravitreal injection of endotoxin induced an inflammation response with a peak at 18 h, reflected in a mean aqueous cell count of 1595 combined with clinical signs of hyperemia, edema in eyelids and anterior chamber cells (grade 3+) and/or fibrin membrane in the anterior chamber. Treatment with both FLB and dexamethasone showed significant decrease of inflammatory response both in clinical examination and total

Table 1 Concentration of intravitreal flurbiprofen as measured in HPLC in specific time points

Time (hours)	Average (ppm) ± SD
0	259.36 ± 118.94
1	131.29 ± 22.97
3	109.87 ± 71.74
12	2.06 ± 0.54
24	2.87 ± 2.09
72	0.30 ± 0.10
168	0.06 ± 0.09

N = three eyes were used at each time point. (SD = standard deviation)

cell count. At 12 h and before any intervention with intravitreal solutions, all rabbit eyes revealed with hyperemia, mild edema in eyelids and anterior chamber cells grading approximately 1+. During the intervals of the intravitreal injections between 12 and 18 h, clinical examination of rabbit eyes showed less hyperemia and anterior chamber cells grading 0.5+ and 1+ when treated with dexamethasone and FLB consecutively. In contrast, control eyes presented with increased inflammatory response with hyperemia, fibrin membrane in some cases, anterior chamber cells 3+ and a hazy vitreous cavity. At 24 h, FLB and dexamethasone reduced the concentration of leucocytes by 96.84% ($p < 0.05$) and 97.44% ($p < 0.05$), respectively (Fig. 2, Table 3).These findings paralleled the findings of clinical examination, with less or no conjunctival hyperemia, no fibrin membrane and anterior chamber cells grading in eyes treated with dexamethasone or FLB at 0.5+. At 24 h, control eyes revealed signs of inflammation, including hyperemia, posterior synehae, iris dilation and fibrin in the anterior chamber and anterior chamber cells at 3+. During indirect fundoscopy, one eye appeared with snow balls in the vitreous cavity. When intraocular drugs were administered, signs of inflammation were less obvious with mild hyperemia being the most prominent finding. Accordingly, fundoscopy revealed no signs of inflammation. Intraocular pressure was within normal limits in all eyes.

Histology

Light microscopy in control eyes demonstrated signs of uveitis; edema and blood stasis in ciliary body, leucocyte concentration on the retina surface, disorganization and morphological alterations in the architecture of the outer nuclear layer. On the contrary, FLB administration decreased significantly the leucocyte concentration on the retina surface with no distortion in the architecture of retina layers and no signs of inflammation in the ciliary body. Dexamethasone showed the same results as FLB. Pigment epithelial cells preserved their contacts with the Bruch's membrane in all specimens. No desquamation or degeneration of pigment epithelial cells was observed (Fig. 3).

Table 2 Pharmacokinetic parameters of intravitreal flurbiprofen

	Flurbiprofen
K_e	0.36
$t_{1/2}$ (hours)	1.92
Cmax (ppm)	259.36
R^2	0.77

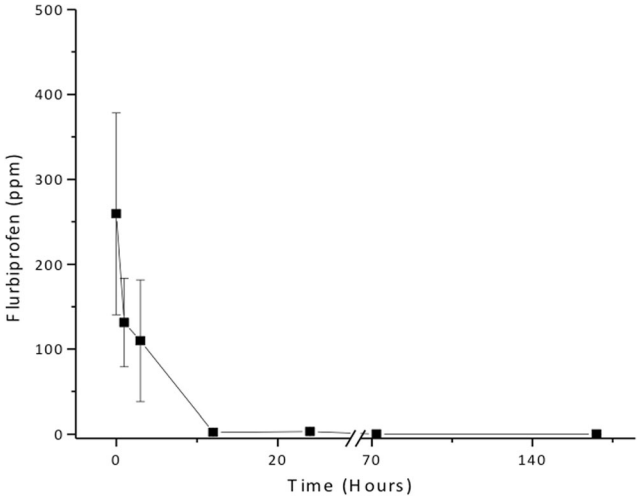

Fig. 1 Bioavailability of intravitreal flurbiprofen after a single injection at short time points. The data represent the mean drug concentration of three samples at each time point. Half-life of the drug is estimated to be 1.92 h

Discussion

Topical administration of NSAIDs has been proved to be sufficient in treating disorders of the anterior segment of the eye [1, 2]. This route of administration does not seem to be similarly effective when the posterior segment is targeted.

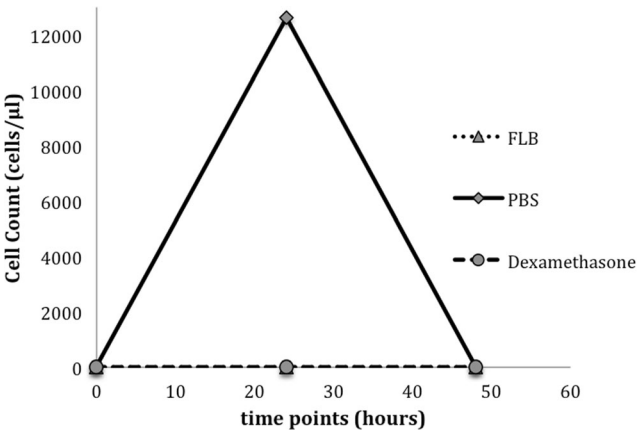

Fig. 2 Uveitis model after injecting flurbiprofen, dexamethasone and PBS (solvent). Flurbiprofen and dexamethasone reduce the inflammatory cells up 96.84% ($p < 0.05$) and 97.44% ($p < 0.05$), respectively, compared with control eyes (PBS)

Table 3 Efficacy of flurbiprofen and dexamethasone after intravitreal injection of endotoxin

Time (hours)	Flurbiprofen (cell/μl) ± SD	Dexamethasone (cell/μl) ± SD	PBS (cell/μl) ± SD
0	0	0	0
24	399.44 ± 86.16	324.16 ± 32.79	12,626.62 ± 233.35
48	127.91 ± 102.10	126.66 ± 66.02	393.88 ± 207.18

N = 5 eyes were used in each group; flurbiprofen, dexamethasone, PBS. Total cell count at time points 24 h and 48 h. Both drugs reduced the inflammatory cells in the anterior chamber compared with controls (PBS). (SD = standard deviation)

Intravitreal delivery of NSAIDs results in significantly higher concentrations inside the eye, limiting the amount of dose compared to systemic delivery. There are data in the literature demonstrating their potential for inflammation control in several entities after intravitreal administration. Ketorolac tromethamine was the first NSAID to be administered in the vitreous cavity in patients with retina pathologies including cystoid macular edema (CME), demonstrating early resolution of inflammation [10]. Several other studies have also reported the therapeutic effect of NSAIDs in uveitic CME [12, 13], in diabetic retinopathy [14, 15] and in choroidal neovascularization [16]. In a recent small case series published by Tsilimbaris et al., an NSAID was administered intravitreally in chronic CME after cataract surgery. Their results showed favorable therapeutic response after repeated daily injections of the drug [16].

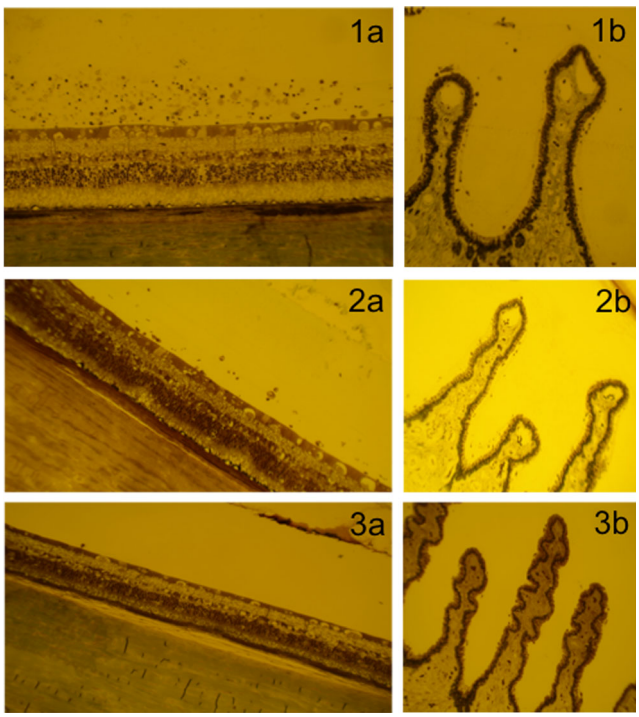

Fig. 3 Light microscopy of the retina and ciliary body 7 days after injection of PBS, flurbiprofen and dexamethasone in the uveitis model. After PBS administration, leucocyte concentration on the retina surface and disorganization of outer nuclear layer observed (1a) edema, leucocytes and blood stasis in the ciliary body (1b). Flurbiprofen (2a, 2b) and dexamethasone (3a, 3b) decreased the presence of leucocytes; the retina and ciliary body remained untouched

In this study, we evaluated the pharmacokinetics and efficacy of FLB. FLB is referred to as a small molecule that inhibits cycloxygenase, a critical enzyme in the inflammatory process, catalyzing the biosynthesis of PGs. As a non-selective inhibitor (COX-1 and COX-2), it results in a decrease of PG secretion. PGs play a vital role in the inflammatory cascade and contribute to pathologies, ranging from pure inflammatory conditions (e.g. uveitis) to the inflammatory component of composite pathologies such as diabetic retinopathy and wet macular degeneration [17, 18]. FLB is already in use as an eye-drop formulation with sufficient control of anterior segment inflammation; its toxicity after intravitreal administration has been evaluated, demonstrating a satisfactory safety profile [5]. To the best of our knowledge, its kinetics and efficacy after intravitreal administration has not been studied yet [19].

The half-life of FLB was found to be 1.92 h. These results are in consistent with reports in the bibliography that studied vitreous clearance of NSAIDs [11, 12]. Because of the short half-life of the drug, repeated injections in short intervals (hours or few days) would be necessary in order to achieve lasting therapeutic levels [15]. Another option could be to increase the concentration of the drug delivered in the vitreous cavity but this could exceed the safe injectable doses. This fact sets an obvious limit for the clinical use of both FLB and most of the other NSAIDs in their current pharmacological form. The development of sustained release formulations could overcome this limit, and represent an obligatory subsequent step for the evolution of intravitreal NSAID agents.

Our results demonstrate that intraocular FLB significantly reduces intraocular inflammation in an animal uveitis model. Clinical signs such as fibrinoid exudation, hyperemia, eyelid edema and total leucocyte count were reduced significantly. In our experimental setting, intravitreal FLB was able to markedly reduce inflammation in a comparable manner to dexamethasone. Dexamethasone's half-life is reported to be 5.5 h and its' action is focused on several pathways in the inflammatory cascade [20, 21]. NSAIDs demonstrate a better safety profile than steroids, with no cataract formation or IOP elevation. As Morales et al. report, FLB is well tolerated and a single intravitreal injection of FLB cause no side effects in a dose up

to 1 mg [5]. The combination of the efficacy data of our study with the safety data from literature make FLB a viable candidate for additional experiments aiming to the development of a clinically useful NSAID agent for intravitreal administration.

In this work we did not include toxicity studies for intravitreal FLB. As a result, electrophysiology was not included in the experimental procedures. We relied on the study of Morales et al., which demonstrated that intravitreal FLB is safe up to 1 mg. For the same reason, we did not include electron microscopy in our study, which could reveal more details about the drug toxicity. A toxicity study is currently underway in our lab to evaluate the toxicity potential of FLB in various pharmacotechnical forms.

In conclusion, intravitreal delivery of FLB proved to be effective in controlling ocular inflammation in an experimental uveitis model. Till today, only corticosteroids have been routinely used intravitreally in order to control inflammation of the posterior segment of the eye. Their availability in a number of sustained release formulations significantly enhances their usability. However, their side effects, such as cataract formation or intraocular pressure elevation, pose serious limitations in their use [3]. Development of an intravitreal sustained release formulation of NSAIDs could give a very attractive alternative to steroids.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

None of the authors has any proprietary interests or conflicts of interest related to this submission. This submission is not being considered simultaneously for publication at any other journal.

Ethical approval All applicable international, national and/or institutional guidelines for the care and use of animals were followed.

References

1. Kim SJ, Schoenberger SD, Thorne JE, Ehlers JP, Yeh S, Bakri SJ (2015) Topical nonsteroidal anti-inflammatory drugs and cataract surgery: a report by the American Academy of ophthalmology. Ophthalmology 122(11):2159–2168
2. Gillies MC, Kuzniarz M, Craig J, Ball M, Luo W, Simpson JM (2005) Intravitreal triamcinolone-induced elevated intraocular pressure is associated with the development of posterior subcapsular cataract. Ophthalmology 112(1):139–143
3. Roth DB, Verma V, Realini T, Prenner JL, Feuer WJ, Fechtner RD (2009) Long-term incidence and timing of intraocular hypertension after intravitreal triamcinolone acetonide injection. Ophthalmology 116(3):455–460
4. Abdel-Aziz AA, Al-Badr AA, Hafez GA (2012) Flurbiprofen. Profiles Drug Subst Excip Relat Methodol 37:113–181
5. Morales AM, Kivilcim M, Peyman GA, Main M, Manzano RP (2009) Intravitreal toxicity of ketorolac tris salt and flurbiprofen. Ophthalmic Surg Lasers Imaging 40(1):38–42
6. Cheruvu NP, Amrite AC, Kompella UB (2008) Effect of eye pigmentation on transscleral drug delivery. Invest Ophthalmol Vis Sci 49(1):333–341
7. Hye IL, Chang IC, Ji YB, Jung EL, So YP, Young HK, Se HK, Yun JL, Choon GJ, Seok YL (2014) Simultaneous determination of flurbiprofen and its hydroxy metabolite in human plasma by liquid chromatography-tandem mass spectrometry for clinical application. J Chromatogr B 971:58–63
8. Bakri SJ, Snyder MMR, Reid JM, Pulido JS (2007) Pharmacokinetics of intravitreal bevacizumab (avastin). Ophthalmol 114:855–859
9. Goldblum D, Fausch K, Frueh BE, Theurillat R, Thormann W, Zimmerli S (2007) Ocular penetration of caspofungin in a rabbit uveitis model. Graefes Arch Clin Exp Ophthalmol 245(6):825–833
10. Serif N, Gurelik G, Hasanreisoğlu M, Yaman H, Akyurek N (2016) Evaluation of Neopterin levels in an Endotoxin-induced experimental Uveitis model. Semin Ophthalmol 31(3):256–260
11. Kim SJ, Toma H, Shah R, Kompella UB, Vooturi SK, Sheng J (2014) The safety, pharmacokinetics, and efficacy of intraocular celecoxib. Invest Ophthalmol Vis Sci 55(3):1409–1418
12. Kim SJ, Doherty TJ, Cherney EF (2012) Intravitreal ketorolac for chronic uveitis and macular edema: a pilot study. Arch Ophthalmol 130(4):456–460
13. Ramezani A, FardEsmaeilpour N, Eskandari A, Rabbanikhah Z, Soheilian R, Soheilian M (2013) Intravitreal diclofenac for refractory uveitic cystoid macular edema. J Ophthalmic Vis Res 8(1):47–52
14. Maldonado RM, Vianna RN, Cardoso GP, de Magalhaes AV, Burnier MN (2011) Intravitreal injection of commercially available ketorolac tromethamine in eyes with diabetic macular edema refractory to laser photocoagulation. Curr Eye Res 36(8):768–773
15. Reis Ado C, Vianna RN, Reis RS, Cardoso GP (2010) Intravitreal injection of ketorolac tromethamine in patients with diabetic macular edema refractory to retinal photocoagulation. Arq Bras Oftalmol 73(4):338–342
16. Kim SJ, Toma HS (2010) Inhibition of choroidal neovascularization by intravitreal ketorolac. Arch Ophthalmol 128(5):596–600
17. Tsilimbaris MK, Tsika C, Kymionis GD (2016) Intravitreal ketorolac for the treatment of chronic cystoid macular edema after cataract surgery. TherClin Risk Manag 12(12):177–182
18. Schoenberger SD, Kim SJ, Sheng J, Rezaei KA, Lalezary M, Cherney E (2012) Increased prostaglandin E2 (PGE2) levels in proliferative diabetic retinopathy, and correlation with VEGF and inflammatory cytokines. Invest Ophthalmol Vis Sci 53:5906–5911
19. Sabiston DW, Robinson IG (1987) An evaluation of the anti-inflammatory effect of flurbiprofen after cataract extraction. Br L Ophthalmol 71(6):418–421
20. Diakonis VF, Tsourdou A, Tzatzarakis MN, Tsika C, Charisis S, Naoumidi I, Plainis S, Tsilimbaris MK (2013) Evaluation of vitreous clearance and potential retinal toxicity of intravitreal lornoxicam (xefo). J OculPharmacolTher 29(7):627–632
21. Gan IM, Ugahary LC, van Dissel JT, van Meurs JC (2005) Effect of intravitreal dexamethasone on vitreous vancomycin concentrations in patients with suspected postoperative bacterial endophthalmitis. Graefes Arch Clin Exp Ophthalmol 243:1186–1189