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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) IN OPHTHALMOLOGY

Dr. Vandana Yadav (MS)*	senior resident, department of ophthalmology, Uttar Pradesh university of medical sciences, Saifai, Etawah. *Corresponding Author
Dr Swati Yadav	Junior Resident, IGMC Shimla, HP.
Dr Srishti Yadav	Junior Resident, AMU, Aligarh.
Dr Ashok Kumar (MD)	Senior Resident, Department Of Pediatrics, UPUMS, Saifai, Etawah.

ABSTRACT This is a review article; we have collected data from PubMed through the available articles. NSAIDS are very commonly prescribed drugs in ophthalmology administered topically and also, used orally. They have analgesic, antipyretic, and anti-inflammatory properties. They inhibit cyclooxygenase enzyme and decrease the synthesis of prostaglandins which can disturb the blood ocular barrier. NSAIDS have a wide variety of uses in post operative cystoid macular oedema, scleritis, allergic conjunctivitis, as analgesic after refractive surgeries, central serous chorioretinopathy and in wet ARMD etc. We have summarized all this information in this review article.

KEYWORDS :

INTRODUCTION

This is a review article; we have compiled this review using articles identified by searching PubMed.

NSAIDS are very commonly prescribed medicines. They have analgesic, antipyretic, and anti-inflammatory properties. [1]

First topically administered NSAID in ophthalmology was Indomethacin which belong to indole chemical class of drugs. Other drugs used topically are phenyl alkanoic acids [Flurbiprofen (0.03%), Ketorolac (0.5%), Suprofen (1%), Nepafenac (0.1%, 0.3%)]. Phenylacetic acid used topically is Diclofenac (1%). [2]

NSAIDS used orally in ophthalmology are indomethacin, ibuprofen, naproxen etc. [3]

Mechanism Of Action

NSAIDS inhibit Cyclo-oxygenase (COX) enzyme. COX catalyze the production of prostaglandins (PGE2, PGD2, PGF2 alpha, PGI2 and Thromboxane A2). Prostaglandins increase the vasodilation and increase vascular permeability with disruption of blood ocular barrier and facilitate leucocyte migration. They also amplify vascular endothelial growth factor (VEGF). NSAIDS inhibit COX enzyme thus, inhibit the production of prostaglandins and help in decreasing intraocular inflammation and retinal edema. COX2 is the main isoform of COX enzyme in RPE cells and it gets upregulated if proinflammatory cytokines increase. COX2 has important role in angiogenesis and is also involved in choroidal neovascularisation and proliferative diabetic retinopathy. [1]

Pharmacokinetics And Pharmacodynamics

NSAIDS get adsorbed in the gastrointestinal tract, get metabolised in liver and are excreted in urine and bile. They reach a peak serum concentration in 1-3 hours. They have a high protein binding capacity (95%), mainly to albumin.[4]

Topically administered NSAIDS get adsorbed systematically by mucosal surfaces and nasolacrimal outflow system.[4]

Aqueous Levels

After topical single application: Diclofenac (0.1%) 82ng/ml (2–4-hour peak), Flurbiprofen (0.03%) 60ng/ml (2-hour peak), **Nepafenac (0.1%) 205.3 ng/ml (peak in 30 minutes),** Amfenac (70.1 ng/ml), Ketorolac (0.4%) 57.5ng/ml (peak in 60min), Bromfenac (0.09%) 25.9 ng/ml. [1]

Nepafenac is a prodrug, a non-charged molecule, it has maximum corneal permeability when compared to other NSAIDS. It gets converted to more potent amfenac by intraocular hydrolases. [4]

Vitreous Levels

Heier et al. observed that patients who received ketorolac (0.4%) 4 times per day, bromfenac (0.09%) two times per day , nepafenac (0.1%) 3 times/day before vitrectomy surgery, vitreous levels were 2.8ng/ml, 0.96ng/ml and 2ng/ml respectively. [4, 5]

Only Ketorolac Has Resulted In Significantly Lower PGE2 In Vitreous Compared To Placebo.

Uses of NSAIDS

There are various uses of NSAIDS in ophthalmology:

Irvine-Gass syndrome: it is postoperative cystoid macular edema (CME), characterised by presence of intraretinal fluid spaces or central macular thickening and can be accompanied by mild photoreceptor detachment on optical coherence tomography (OCT). Fluid accumulates in outer plexiform and inner nuclear spaces and creates cystic intraretinal spaces that coalesce to large fluid cavities. Prolonged CME can cause lamellar hole and persistent subretinal fluid. On fluorescein angiography (FA) early phases show leakage.[6]

Its peak incidence is 6 weeks after surgery, found in 1-2% patients.[6]

Risk factor for post-surgical CME include history of uveitis, diabetes mellitus (DM), presence of epiretinal membrane and use of topical drugs for glaucoma.[6]

In diabetes mellitus breakdown of blood retinal barrier occur secondary to diabetic vasculopathy. Severity of CME depend on duration, severity and control of DM. Diabetic retinopathy increase the risk of CME by 2-3 times.[7]

NSAIDS are anti-inflammatory drugs found to be highly effective in reducing post-surgical inflammation and incidence of CME, and this is supported by clinical and epidemiological research that provide data on the spontaneous resolution of CME with the use of NSAIDS.[6]

Nepafenac (0.1% 3times/day or 0.3% once/day) is started 1 day before surgery, continued (30-120 minute) prior on the day of surgery and after surgery given for 90 days. It has shown efficacy in prevention and management of CME.[7]

Bromfenac (0.07% and 0.09%) has also shown efficacy in the prevention and treatment of CME.[8]

Scleritis: it is a highly symptomatic inflammatory disease of sclera. Systemic NSAIDS are mainstay treatment for acute scleritis. [3] Topical NSAIDS have some success in episcleritis management but they are not recommended for acute scleritis due to risk of scleral melting. [3,9,10]

For severe scleritis, necrotizing scleritis and vasculitis associated scleritis NSAIDS are not ideal first line agents, systemic steroids and immunomodulatory therapy to be considered for such cases. [3]

Allergic conjunctivitis: it is characterised by itching, burning, tearing and lid edema on exposure to airborne allergens. Itching is due to release of histamine, prostaglandins and leukotrienes. NSAIDS inhibit the release of prostaglandin which lower the threshold of histamine induced itching. Ketorolac (0.5%) significantly reduce ocular itching. [2]

Inhibition of intraoperative miosis: topical flurbiprofen (0.03%), indomethacin (1%), diclofenac sodium (0.1%) and suprofen (1%) are used. [2]

After refractive surgeries: NSAIDS are used for their analgesic effect. Diclofenac sodium used in **photorefractive keratectomy** (PRK), it has analgesic and anaesthetic effect. It reduces corneal sensitivity. [2] After **radial keratotomy** no statistical difference in efficacy of topical ketorolac compared to diclofenac in reducing discomfort. [2,11]

Episcleritis and corneal limbal ulcers: NSAIDS are used due to their analgesic and steroid sparing effect like diclofenac (0.1%). [2]

Indomethacin does not has significant analgesic activity. [2,12]

Non-infectious Uveitis: used for the management of macular edema in non-infectious uveitis.[13]

CSCR (central serous chorioretinopathy): CSCR may develop due to increased permeability of choroidal vessels with increased hydrostatic pressure, loss of RPE function and lead to accumulation of subretinal fluid. Spontaneous serous detachment of neurosensory retina occur in the macular region. Excessive steroid use and endogenous cortisol production can impair the RPE function, choroidal vascular autoregulation, hypercoagulability and augmented platelet aggregation. NSAIDS have protective effect by reducing the prostaglandin release, reduced aldosterone secretion and anticoagulant effects. [14]

Wet ARMD (age related macular degeneration): for choroidal neovascularisation, VEGF is the principle mediator. COX2 can be detected in the human choroidal neovascular membranes, COX promote angiogenesis. NSAIDS inhibit COX enzyme and thus decrease VEGF expression. [1]

Gomi et al. concluded that combination of Bromfenac (0.1%) and intravitreal Ranibizumab significantly reduced the number of anti VEGF injections, compared to monotherapy with intravitreal Ranibizumab. [1,15]

So, these are the various uses of NSAIDS in ophthalmology.

Side Effects Of NSAIDS

Burning, stinging and ocular irritation can occur. Hypersensitivity reactions can occur like itching, redness, photosensitivity, keratitis punctata etc. to NSAIDS especially in patients with asthama, urticaria. Prostaglandins decrease intraocular pressure by increasing the uveoscleral outflow, NSAIDS can interfere with the hypotensive effect of prostaglandins. There are no adequate studies in pregnant women. So, avoid the use of NSAIDS in pregnancy.[2] NSAIDS can increase the bleeding tendency if used in conjugation with surgery. [2,16]

CONCLUSION

NSAIDS are used in ophthalmology in various diseases, they decrease the inflammation and have analgesic effect. Act by inhibition of COX enzyme and decrease the production of prostaglandins and thus, help in maintaining the blood ocular barrier. Used in post-surgery CME, scleritis, uveitis, episcleritis, allergic conjunctivitis, CSCR, wet ARMD etc. burning, stinging and irritation can occur and few hypersensitivity reactions were noted in allergic patients. NSAIDS can be used for various diseases, just avoid their use during pregnancy as there are no adequate studies.

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