Chapter 8
Steroidal and Nonsteroidal Anti-inflammatory Agents for Ocular Use

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Abstract Multiple factors cause ocular inflammation in various anatomical regions of the eye. Such inflammations are usually tackled with limited symptomatic treatment modalities. The poor prognosis of or long-standing ocular inflammation can even culminate into permanent loss of vision. Ocular inflammation can be majorly divided into infections and non-infections conditions. This chapter deals with the various ocular anti-inflammatory agents used in conditions like uveitis, ocular manifestations of Behchets disease, diabetic retinopathy and allergic conditions leading to ocular surface inflammations.

8.1 Introduction

Ocular inflammation is a common condition, albeit multifactorial and originating in different anatomical regions of the eye, that is usually tackled with limited symptomatic modalities. The prognosis of long-standing ocular inflammation can even be permanent loss of vision.

One of the most common inflammatory eye diseases is uveitis. Uveitis can occur either as an autoimmune disorder or as a result of injury, infection, or exposure to toxins. The most common symptoms of uveitis are flares, redness,

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photophobia, floaters, blurred vision, and sometimes pain. Untreated uveitis can lead to serious sequelae such as permanent vision loss. It accounts for approximately 10 % of visual handicap in the Western World or 30,000 new cases of blindness at an incidence of 20–52 cases per 100,000 person-years (Larson et al. 2011).

The other noninfectious ocular inflammation is Behcet's disease (BD) that is chronic, relapsing, multisystem disorder characterized by ulcers of the oral and genital mucocutaneous tissue, skin lesions, and nonerosive arthritis.

Diabetic retinopathy, a complication of chronic long-standing diabetes mellitus, is also marked by inflammation of eye.

Diabetic retinopathy is characterized by appearance of microaneurysms, increased vascular permeability, capillary occlusion, and fibrous and neovascular proliferation.

The inflammatory processes play a considerable role in the pathogenesis and progression of DR (Kaštelan et al. 2013). Studies have shown marked presence of inflammatory factors in systemic as well as local (vitreous and aqueous fluid) areas with significant correlation to the development of impaired vision. The Early Treatment DR Study and the Dipyridamole Aspirin Microangiopathy of Diabetes Study have shown that the development of retinal microaneurysms is significantly minimized in patients with early stage of DR when treated with a high dose of aspirin (900 mg/day). Topical administration of COX-2 inhibitor was shown to reduce signs of DR similar to its systematic application without the side effects and holds promise for its therapeutic benefit.

Ocular inflammation is also common after ophthalmic surgery, particularly after surgical removal of cataracts combined with intraocular lens (IOL) implantation. The condition manifests as mild iritis, corneal edema, and flare in the anterior chamber of the eye, accompanied by hyperalgesia. If left untreated, postoperative inflammation can lead to suboptimal vision results or complications such as cystoid macular edema (CME).

Dry eye syndrome has been described as multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface that is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. It is most prevalent among the elderly and postmenopausal women. Chronic dryness of the surface of the eye can lead to neurogenic inflammation, activation of T cells, and release of inflammatory cytokines into the lacrimal glands, tear fluid, and conjunctiva. These inflammatory mediators are known to cause gradual dysfunction and destruction of the lacrimal glands and impairment of conjunctival epithelium.

Literature evidences that oxidative stress is the primary initiating event that leads to the inflammatory state of ocular surface. Thus, oxidative stress with associated inflammatory process can trigger severe injury of retina, cornea, conjunctiva, and lacrimal gland.

8.2 Steroidal and Nonsteroidal Anti-inflammatory Agents for Ocular Inflammation

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8.2.1 Corticosteroids

Corticosteroids have a broad mechanism of action. They inhibit phospholipase A2, an enzyme that converts membrane phospholipids to arachidonic acid. Thus, the inhibition of the cyclooxygenase and lipoxygenase pathways dramatically reduces the formation of all eicosanoids, which are the active mediators of inflammation. Corticosteroids effectively suppress both the early (capillary dilation, increased vascular permeability, recruitment of leukocytes) and late (deposition of fibrin, proliferation of inflammatory cells and chemokines) phases of inflammation.

Local corticosteroids may be used either topically (for anterior uveitis) or as periocular and intravitreal injections, or as implant devices (for inflammation of posterior segment) and remain the drugs of choice in management of ocular inflammation. Systemic corticosteroids are reserved for chronic uveitis involving the posterior segment, invariably affecting both eyes. However, chronic use of corticosteroid therapies is known to cause glaucoma, cataract, impaired glucose tolerance, hypertension, fluid retention, osteoporosis, mental disturbance, impaired wound healing, gastrointestinal bleeding and perforation, thromboembolic disorders, and weight gain. Of these, increased IOP is of most importance as it is understood to be due to structural and biochemical changes in the trabecular meshwork leading to rise in the resistance to aqueous humor outflow. The incidence of steroid-induced IOP elevation is quite high in as many as 18–36 % of users. Older corticosteroids, such as prednisolone and dexamethasone, are associated with a greater impact on IOP compared to newer corticosteroids. The limitations of chronic use of steroids, vis-a-vis lack of efficacy and need for reinjections, have led to the development of novel sustained-release intravitreal steroid delivery methods. These formulations have lower dose of corticosteroids and, therefore, less secondary side effects.

Multiple formulations like oral prednisone, intravenous methylprednisolone sodium succinate, topical prednisolone acetate or difluprednate, and intravitreal triamcinolone are preferentially used as they offer the benefit of avoiding systemic complications (Geltzer et al. 2013).

Recently, fluocinolone acetonide implant (Retisert) has been developed to deliver corticosteroid for up to 30 months for chronic noninfectious posterior uveitis. Dexamethasone implant for intravitreal use (Ozurdex) has also been approved by the FDA for the treatment of noninfectious posterior uveitis. It is available as 0.7 mg biodegradable implant that delivers extended release of dexamethasone through solid polymer delivery system. Although dexamethasone and prednisolone acetate offer good anti-inflammatory efficacy, their use suffers from clinically

significant increase in IOP (up to 10 mmHg). In contrast, corticosteroids such as loteprednol etabonate, a novel C-20 ester-based derivative of prednisolone, offer potent anti-inflammatory efficacy, with limited adverse impact on IOP. Loteprednol etabonate (0.5 %) has been established as effective treatment of postoperative inflammation and resolving anterior chamber cells and flare (Amon and Busin 2012).

Another prednisolone derivative, difluprednate with structural modifications that include the addition of fluorine atoms at C-6 and C-9 positions, a butyrate ester at the C-17 position, and acetate ester at the C-21 and C-20 ketone moiety, is significantly effective in controlling secondary events of ocular inflammation like photophobia, chemosis, and corneal edema. The incidence of clinically significant increase in IOP is low.

The efficacy of loteprednol etabonate, rimexolone, and difluprednate in resolving ocular inflammation is similar. The difference lies in the degree of side effect like corticosteroid-induced ocular hypertension and is often the determining factor in clinical use.

8.2.2 Antimetabolites

Antimetabolites refer to a class or drugs which inhibit nucleic acid synthesis to inhibit cell proliferation. Drugs belong to this class include methotrexate, azathioprine, and mycophenolate mofetil.

Methotrexate was first introduced in 1948 as an antineoplastic agent. It is a folate analogue that acts by inhibiting dihydrofolate reductase. It interferes with the synthesis of thymidylate and purine nucleotide, to inhibit the growth of rapidly dividing cells. The most serious side effects of methotrexate include hepatotoxicity, cytopenias, and interstitial pneumonitis. Monitoring of liver function tests is required during treatment. It is teratogenic and thus contraindicated in pregnancy.

Azathioprine is widely used in organ transplantation, inflammatory bowel disease, systemic lupus erythematosus, and other autoimmune conditions. It is a prodrug of 6-mercaptopurine, a purine nucleoside analogue that interferes with DNA replication and RNA transcription. It also inhibits actively dividing immune cells to restrain inflammatory process.

Mycophenolate mofetil (MMF) is commonly used in management of organ transplant rejection and other autoimmune conditions. Its mechanism of action is selective inhibition of inosine-5-monophosphate dehydrogenase in the de novo purine synthesis pathway. As B and T lymphocytes depend on the de novo pathway for proliferation, its selective inhibition effectively curtails inflammatory state. MMF has been shown to be effective in combination with steroids or another immunomodulatory treatment as well as monotherapy.

8.2.3 T-Cell Inhibitors

This class of agents includes cyclosporine, tacrolimus, and sirolimus.

Cyclosporine is an 11 amino acid peptide derived from fungus. Cyclosporine acts by forming a complex with cyclophilin which binds calcineurin that then inhibits the cytosolic translocation of nuclear factors. Consequently, there is preferential inhibition of antigen-triggered signal transduction of T lymphocytes. It is available in two formulations, as oil-based gelatin capsules (Sandimmune, Novartis Pharmaceuticals) and a microemulsion (Neoral, Novartis Pharmaceuticals). Cyclosporine has been used safely in children with severe, sight-threatening uveitis. The adverse effects of cyclosporine therapy include gastrointestinal upset, metabolic abnormalities, paresthesias, tremor, gingival hyperplasia, and hirsutism.

Voclosporin is a calcineurin inhibitor that has been developed for the treatment of uveitis. It has been shown to be more potent and less toxic than cyclosporine. In extensive placebo-controlled clinical studies, voclosporin has been reported to improve vitreous haze that is part of active posterior disease. It significantly reduced eye inflammation but failed to meet the primary endpoint of all-cause therapeutic failure. In the condition of anterior inflammation, voclosporin failed to establish itself from placebo.

Tacrolimus or FK506 is a macrolide isolated from the soil fungus *Streptomyces tsukubaensis* that was originally used in solid organ transplantation. It has a similar mechanism of action to cyclosporine and binds to an intracellular binding protein, FK-binding protein, that associates with calcineurin and thus inhibits activation of T cells and production of cytokines.

Sirolimus (Rapamune) is another immunosuppressive drug. Its binds to FK-binding protein-12 (FKBP-12) to form a complex that binds to and inhibits the activation of the mammalian target of sirolimus (mTOR) to suppress cytokine-driven T-cell proliferation.

8.2.4 Alkylating Agents

Cyclophosphamide and chlorambucil belong to the class of drugs called alkylating agents as they act by alkylating DNA leading to DNA cross-linking and inhibition of DNA synthesis. Although they were originally developed for the treatment of cancers, they are now widely being used for management of rheumatologic conditions. Owing to their serious, life-threatening side effects, their use is limited to severe, sight-threatening uveitis.

Cyclophosphamide, a mustard gas derivative, alkylates the purines of DNA and RNA resulting in cross-linking and impaired cell division. Thus, the number of inflammatory cells like T and B lymphocytes is reduced.

8.2.5 Biologic Agents

Conventional therapy with corticosteroids and immunosuppressive agents may not be sufficient to control ocular inflammation or prevent non-ophthalmic complications in refractory patients. Off-label use of biologic response modifiers has been studied as primary and secondary line of therapy and reported to be very useful in such conditions. Strategies for biologics employ formulating new drugs that target specific receptors, cytokines, or signaling pathways (Pasadhika and Rosenbaum 2014).

8.2.5.1 Anti-Tumor Necrosis Factor-α (TNF-α)

TNF-α is a well-known proinflammatory cytokine that has been shown to play a key role in pathogenesis of inflammatory diseases. Thus, inhibiting TNF-α with antibodies has been a well-accepted strategy to suppress autoimmune uveitis (Karampetsou et al. 2010). TNF-α inhibitors include infliximab, a chimeric mAb, and adalimumab, a fully humanized IgG1 mAb, against TNF-α (Verma et al 2013). Certolizumab pegol and golimumab have only been recently introduced and there is limited clinical experience with them. Other agents such as abatacept, canakinumab, gevokizumab, tocilizumab, and alemtuzumab hold promise for the treatment of uveitis in the future. Systemic administration of anti-TNF-α agents has shown encouraging preliminary results in uveitic and diabetic cystoid macular edema and age-related macular degeneration.

Infliximab (Remicade) is a 149 kDa chimeric IgG1 monoclonal antibody composed of human constant region of IgG1 and murine variable binding site for TNF-α. It has been approved for use in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis and Crohn's disease. It is well accepted for management of various subtypes of refractory uveitis and retinal vasculitis, especially Behcet's disease-related eye conditions and the uveitis associated with juvenile idiopathic arthritis. Infliximab in BD-associated uveitis is advocated as an add-on therapy to DMARDs. The combination significantly reduced the frequency of uveitis flares compared to administration of DMARDs alone.

Etanercept (Enbrel) is a fusion protein consisting of the binding part of the human type II receptor of TNF-α linked to the Fc portion of IgG1a. It is a blocker of soluble TNF-α receptor that has also been investigated as subcutaneous injection (25 mg/week). But it has been found to be less effective than infliximab or adalimumab in the treatment of uveitis. In retrospective study, when infliximab was compared to etanercept, the number of recurrences and ocular inflammation was improved with former as compared to latter.

Apremilast, a selective cytokine inhibitory drug, inhibits phosphodiesterase IV and TNF-α production to suppress the immune response. It is currently in phase II clinical trials for Behcet's disease. As the drug is projected for oral administration, the need for injection is circumvented and reduces cost considerably.

ESBA-105 is a topical anti-TNF-α single-chain antibody and possesses good anterior and posterior intraocular penetration. It is under development for the treatment of ocular conditions including uveitis and diabetic retinopathy.

8.2.5.2 Cytokine Receptor Antibodies

Daclizumab is a humanized monoclonal antibody directed against the alpha subunit of the interleukin-2 receptor (CD25) present on activated T cells. The drug is also approved for management of renal allograft rejection and autoimmune diseases such as multiple sclerosis and human T-cell leukemia virus-1-associated T-cell leukemia. The drug can be administered as 1–2 mg/kg infusions every 2–4 weeks. Side effects include rashes, edema, granulomatous reactions, viral respiratory infections, elevated liver enzymes, and leukopenia.

Rituximab, a chimeric monoclonal antibody against CD20, a B-cell marker, results in depletion of B cells. It was originally developed for the treatment of B-cell lymphomas and now finding application in ocular inflammation.

MM-093, a recombinant human alpha-fetoprotein, has recently completed phase II study for sarcoid or birdshot uveitis.

8.2.6 Antiangiogenic Therapy

Vascular endothelial growth factor (VEGF) is a potent vasoactive cytokine that is involved in the breakdown of blood-retinal barrier and angiogenesis in the ischemic retina. The VEGF levels are significantly elevated in patients with DME and its intravitreal concentration increases with the progression of DR. Antiangiogenic therapy acts to reduce vascular permeability, reduce the breakdown of the blood-retinal barrier, inhibit leukocyte adhesion to vascular walls, and inhibit VEGF gene transcription and translation and therefore finds use in ocular inflammatory conditions (Geltzer et al. 2013).

Bevacizumab (Avastin) and ranibizumab (Lucentis) are also monoclonal antibodies to vascular endothelial growth factor (VEGF). Ranibizumab was designed specifically for ocular use and received FDA approval for the treatment of choroidal neovascularization in age-related macular degeneration. Bevacizumab is increasingly finding off-label use for ocular diseases.

Ranibizumab (Lucentis), a recombinant humanized antibody fragment, is active against all isoforms of VEGF-A and approved for the treatment of exudative AMD and DME.

8.2.7 Blocking Oxidative Stress

As a key mediator in inflammation, oxidative stress serves as an important target for anti-inflammatory therapy. The etiology of ocular inflammation involves free radical-mediated oxidative damage, hypoxia, decreased blood supply to ocular tissues, angiogenesis, increased vascular permeability, and leakage of vascular contents.

Flavonoids have been attributed with multi-thronged action including antioxidant, antiangiogenic, reducing fluid retention, and strengthening capillary walls that together contribute to anti-inflammatory activities. Bioflavonoids have been found effective in the prevention and treatment of diabetic retinopathy, macular degeneration, and cataract (Majumdar and Srirangam 2010). Some of the common bioflavanoids that have been documented for their anti-inflammatory action are quercetin, apigenin, hesperidin, hesperetin, luteolin, epigallocatechin gallate, epicatechin gallate, rutin, cyanidin, naringenin, myricetin, chrysin, eriodictyol, and kaempferol.

Flavanoids are hypothesized to act as antioxidant through various actions such as:

(a) By scavenging the free radicals directly—Flavanoids are also known as "quenchers" due to their low redox potential or high reactivity that may be attributable to the presence of hydroxyl groups. Flavonoids are capable of reducing the highly oxidizing free radicals (e.g., superoxide, peroxyl, alkoxyl, and hydroxyl) to form stable, less-reactive radicals.
(b) By inhibiting the nitric oxide production—Nitric oxide (NO) is produced by several types of cells including endothelial cells and macrophages. The inducible nitric oxide synthase (iNOS) is understood to be responsible for the production of high concentrations of NO during oxidative damage. Further, NO reacts with free radicals to generate the highly reactive and damaging peroxynitrite. Flavonoids through their free radical-scavenging properties can prevent the generation of peroxynitrite. They also inhibit iNOS directly and thereby decrease production of NO.
(c) By inhibiting certain enzymes—Flavonoids can inhibit the enzymes such as xanthine oxidase and protein kinase C that are responsible for the production of superoxide anions. They are also capable of inhibiting other enzymes involved in ROS generation such as cyclooxygenase, lipoxygenase, microsomal monooxygenase, glutathione S-transferase, mitochondrial succinoxidase, and NADH oxidase.
(d) By chelating trace elements—Flavonoids are good chelaters of trace elements, like free iron and copper, that are potential enhancers of ROS generation and important in oxygen metabolism.

The major pharmacokinetic limitation of flavonoids is their poor oral bioavailability due to poor intrinsic transmembrane diffusion characteristics, poor solubility, and intestinal and hepatic metabolism. The ocular bioavailability of the flavonoids depends on the formulation and on the route of administration. When administered by the oral route, diffusion of the hydrophilic metabolites from the plasma into the neural retina is severely restricted by the blood-retinal barriers.

Curcumin is also reported for anti-inflammatory properties that are linked to its ability to downregulate the expression of the IκBα gene; cyclooxygenase-2 gene (COX-2); prostaglandin E2 (PGE2); interleukin-1, interleukin-6, and interleukin-8 (IL-1, IL-6, IL-8); and tumor necrosis factor-α (TNF-α). Curcumin also exhibits antioxidant properties and was found useful in chronic anterior uveitis, diabetic retinopathy, glaucoma, age-related macular degeneration, and dry eye syndrome (Pescosolido et al 2014).

8.2.8 Newer Strategies

Renin-angiotensin system (RAS) is well established in the pathogenesis of diabetes and hypertension-induced retinal inflammation. Further, it also activates pathways leading to oxidative stress and AGEs. Hence, blocking RAS is fast emerging as promising target in the management of diabetic retinopathy. Specifically, blockade of AT1R (losartan, candesartan) and angiotensin-converting enzyme inhibitor (Enalapril) has been shown to prevent oxidative stress, inflammation, and vascular damage in diabetic retinopathy. Further studies are ongoing to evaluate the clinical benefits of blocking RAS in ocular inflammation.

8.3 Ocular Allergy and Its Pharmacotherapy

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8.3.1 Introduction

Allergic disorders of ocular surface are a group of immune-mediated inflammatory reactions that generally involve conjunctiva, lids, lid margins and lacrimal system. The cornea is relatively protected due to its anatomical, physiological, and immunological properties. Various clinical forms of ocular allergy include seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VAC), atopic keratoconjunctivitis (AKC), giant papillary conjunctivitis, and drug-induced or contact dermatoconjunctivitis. The acute forms of allergic conjunctivitis, SAC and PAC, involve type I hypersensitivity reaction. On the other hand, more chronic conditions such as VAC and AKC involve type IV hypersensitivity reactions.

The allergic reactions typically develop through 3 phases. The first phase of "sensitization" begins upon exposure of ocular surface to allergens. The antigen-presenting cells (APCs) in conjunctival epithelium such as dendritic cells phagocytize the allergen. After processing within APCs, the peptide fragments of allergen are expressed on the cell surface in association with major histocompatibility complex (MHC) class II molecule. The allergen-MHC complex interacts with T-helper (Th) cells causing their maturation to Th type 1 (Th1) or Th type 2 (Th2) cells, of which Th2 cells, in particular, play a significant role in allergic response. APC-Th2 interaction results in production of cytokines, which interact with naive B cells stimulating production of immunoglobulin E (IgE)-type antibodies. IgE binds to its high-affinity receptors on the surface of basophils and mast cells. Upon subsequent exposure to same allergen, its interaction with IgE on mast cells and basophils results in increased membrane permeability to calcium ions (Ca^{++}) and subsequently, there is mobilization of Ca^{++} from intracellular stores. Significant amount of IgE-antigen interaction, hence, leads to degranulation of mast cells and basophils releasing inflammatory mediators such as histamine, serotonin, leukotriene C4, prostaglandin D2, platelet-activating factor, tryptase,

chymase, cathepsin G, and other eosinophil and neutrophil chemoattractants. These mediators lead to "early-phase reaction" often characterized by redness, itching, and tearing. Exposure to large doses of allergen leads to more persistent "late-phase reaction." This reaction is associated with significant recruitment of inflammatory cells, particularly the eosinophils. In the chronic form of ocular allergy, mast cells also relocate from the substantia propria to the epithelial surface of conjunctiva and play a significant role in the development of allergic reactions. In both the early- and late-phase reactions, mast cells and basophils release histamine, which is the major inflammatory mediator in ocular allergic reaction.

8.3.2 Histamine and Histamine Receptors

Histamine is a biologically active endogenous amine that affects the activity of a variety of cells. Histamine exerts its biological effects through specific G-protein-coupled cell surface receptors that are of 4 types. H1 histamine receptors are ubiquitous in distribution and play a central role in immune and inflammatory responses. Stimulation of H1 receptors results in smooth muscle contraction except in vessels where they cause vasodilation. In the eye, they have significant impact on sensory signaling (Abelson and Schaefer 1993). H2 histamine receptors are predominantly present in gastrointestinal mucosa. To a lesser extent, they are also present in the blood vessels, myocardium, mast cells, and brain. In the eye, H2 receptors are almost exclusively located in association with blood vessels and, hence, have a greater impact on the redness rather than the itching associated with conjunctivitis (Abelson and Udell 1981). H3 histamine receptor is expressed throughout the central nervous system and acts primarily to modulate the function of other signaling molecules such as GABA, serotonin, and dopamine (Esbenshade et al. 2008). It has also been found in nasal mucosa and may play a role in rhinoconjunctivitis (Yokota et al. 2008). H4 histamine receptor is expressed primarily in immune cells such as mast cells and leukocytes and is involved in inflammation and allergy. It has been shown to play a role in chemotaxis and cytokine production during inflammatory reactions (Leite-de-Moraes et al. 2009). It is also expressed by some T cells, including CD4+ T cells (Saravanan et al. 2011). In the eye, H4 receptors are co-localized with H1 receptors and may be as important as H1 receptors in mediating ocular allergic responses (Thurmond et al. 2008).

8.3.3 Treatment of Ocular Allergies

Aim of the treatment in ocular allergies is to provide symptomatic relief, to alleviate the underlying cause and to treat complications in severe forms of allergy. Patients are advised to avoid contact with allergen, if it is known. Cold compresses help in relieving pruritus. Patients are also advised to keep the topical medications refrigerated as the cold drops provide symptomatic relief. Tear substitutes are prescribed as they provide relief by diluting and/or washing out the allergen and inflammatory mediators from ocular surface.

Several groups of drugs are used in the treatment of ocular allergies. Use of topical NSAIDs and corticosteroids has previously been discussed. Ocular decongestants are used to whiten the eye and provide rapid relief. Considering the role of mast cells, basophils, and histamine in ocular allergy, antihistamines, mast cell stabilizers, and drugs with dual action form the mainstay of treatment.

8.3.3.1 Ocular Decongestants

Topical sympathomimetics are used as ocular decongestants. They relieve hyperemia, watering, and irritation by causing local vasoconstriction. The commonly used drugs in this class are phenylephrine and imidazole derivatives.

Phenylephrine

Phenylephrine is a direct-acting α-adrenoreceptor agonist (refer Chap. 6 for detailed pharmacology). The ophthalmic preparations of phenylephrine are available in the concentration range of 0.12–10 %. Concentrations greater than 0.125 % cause mydriasis and are used for dilating the pupil. At 0.125 and 0.12 % concentration, phenylephrine produces little or no effect on pupil (Kubo et al. 1975) but does produce vasoconstriction of the conjunctival vessels. Hence, at this concentration, it is used as ocular decongestant. It can also be added to other medications such as antihistamines and antibiotics. Use of phenylephrine requires caution, particularly in those with angle-closure glaucoma.

The ophthalmic solution of phenylephrine is clear and colorless; however, it turns darker with time upon exposure to air, light, and heat due to oxidation. Such oxidized solutions should not be used. It is also important to follow manufacturer's instructions regarding expiry dates as the solution may lose activity even before any visible color change.

The topical side effects such as pain, stinging, and lacrimation are more common at higher concentrations of phenylephrine. It can cause rebound conjunctival congestion. Systemic absorption of significant amount of phenylephrine can cause hypertension, headache, tachycardia or reflex bradycardia and blanching of skin. It has also been reported to cause dermatoconjunctivitis.

Imidazole Derivatives

Imidazole derivatives include naphazoline, tetrahydrozoline, and oxymetazoline. They cause constriction of conjunctival vessels due to α-adrenoreceptor agonistic action and hence are used as ocular decongestants. Naphazoline 0.1 % causes constriction of superficial conjunctival vessels without significantly affecting deeper scleral vessels. It may slightly dilate the pupil but does not affect the accommodation. Oxymetazoline 0.25 % has been shown to relieve the symptoms of allergic conjunctivitis effectively (Duzman et al. 1986) and the relief may last for 6 h. Tetrahydrozoline 0.1 and 0.05 % also provides rapid

relief of symptoms without affecting the pupil size and intraocular pressure (Grossmann and Lehman 1956; Menger 1959).

Few studies have compared the effects of different decongestants. In one of the studies involving 20 patients with nonspecific allergic conjunctivitis, 0.01 % oxymetazoline was found to be superior to 0.01 % naphazoline in relieving the symptoms of conjunctivitis (Nayak et al. 1987). However, naphazoline 0.2 % produced greater conjunctival blanching compared to tetrahydrozoline 0.05 % and phenylephrine 0.12 % (Abelson et al. 1980). A significant difference favoring oxymetazoline was also observed for the duration of action (Rybiczka and Mauracher 1983).

The topical application of the above agents has been reported to cause significant systemic adverse effects such as change in heart rate or blood pressure. Ocular side effects such as pupillary dilation and increase in intraocular pressure may occur with naphazoline. Prolonged and repeated use of these agents may cause ocular xerosis. Rebound congestion with the use of these agents has not been reported.

8.3.3.2 Antihistamines

H1 antihistamines are particularly useful in the treatment of ocular allergies. H1 antihistamines are now considered to act as inverse agonists and not, as previously thought, as antagonists of histamine. Stimulation of the H1 receptor, a Gq/11-coupled GPCR, classically activates inositol phospholipid signaling pathways resulting in formation of inositol triphosphate and diacylglycerol which leads to an increase in intracellular calcium. H1 antihistamines prevent the effects of H1 receptor stimulation by inhibiting activation of the intracellular signaling pathways. They also modulate the activity of transcription factor NF-κB, inhibit intracellular adhesion molecule-1 (ICAM-1) expression and the effects of bradykinin (Leurs et al. 2002).

H1 antihistamines are grouped into two classes: first-generation (older) drugs and second-generation (newer) drugs. The major differentiating property of the two groups of H1 antihistamines is their ability to cross blood-brain barrier (BBB). First-generation drugs easily cross BBB and hence cause CNS-related adverse effects. Second-generation drugs are largely devoid of CNS-related adverse effects as they do not cross BBB. Additionally, first-generation drugs also block other autonomic receptors and hence cause a range of other adverse effects. The topical route is the preferred choice for the treatment of ocular allergies as it directly delivers the drugs to target site, shortening the onset of action. Additionally, smaller concentrations of drugs are required compared to systemic administration.

Topical Antihistamines

The most widely used first-generation topical antihistamines are antazoline (0.5 %) and pheniramine (0.3 %). Levocabastine (0.05 %) and emedastine (0.05 %) are the second-generation antihistamines available for topical use. Often, they are used in combination with sympathomimetics. After topical application, they spread in the precorneal tear

film and get distributed to conjunctiva and cornea. They may be absorbed systemically through conjunctival vessels and through nasal and oropharyngeal mucosa.

These agents effectively control hyperemia and itching. The efficacy of emedastine and levocabastine in the prevention and treatment of allergic conjunctivitis has been assessed. It was observed that both drugs are significantly more effective than placebo and emedastine was more effective than levocabastine (Verin et al. 2001).

Topical antihistamines are generally well tolerated. They may cause transient burning or stinging upon instillation, eyelid edema, and ocular irritation. They may also cause bad taste, blurred vision, corneal infiltrates, corneal staining, dermatitis, dry eye, foreign body sensation, hyperemia, keratitis, pruritus, rhinitis, sinusitis, and tearing. Systemic adverse effects after local application are not common; however, indiscriminate use may result in the adverse effects as seen with the administration of oral antihistamines.

Oral Antihistamines

Several oral antihistamines, both first and second generation, are available for treatment of ocular allergies; however, due to unfavorable therapeutic index of first-generation agents, second-generation antihistamines are the preferred class (del Cuvillo et al. 2006). The second-generation antihistamines that have commonly been used include levocetirizine, desloratadine, rupatadine, ebastine, cetirizine, loratadine, fexofenadine, and mizolastine.

Oral antihistamines are well absorbed from gastrointestinal tract. They are widely distributed and achieve the peak plasma concentration in 1–2 h. Symptomatic relief may appear in 30 min–1 h and the effect generally lasts for 12 h or more. The effects of first-generation agents are short lasting. First-generation agents cross the BBB, whereas second-generation agents do not cross BBB due to their poor lipophilicity and also because they are substrates of P-glycoprotein reverse transporter in BBB. They are metabolized by cytochrome P450 enzymes and the metabolites are excreted in urine within 24 h. Metabolites of some agents, like hydroxyzine, terfenadine, and loratadine, retain the activity of parent compounds.

Oral antihistamines may be particularly useful in patients with rhinoconjunctivitis. Although topical antihistamines administered to ocular surface may also be used, oral antihistamines more effectively relieve the nasal symptoms (Spangler et al. 2003; Crampton 2003). All of them have been shown to effectively relieve the symptoms of perennial and seasonal rhinoconjunctivitis. Ebastine was shown to be more effective than loratadine in relieving symptoms of seasonal allergic rhinoconjunctivitis (Ratner et al. 2005). The safety of desloratadine, rupatadine, ebastine, and mizolastine in children is not established.

The adverse effect profile of second-generation antihistamines is considerably better than first-generation agents. As the second-generation agents do not cross BBB, hence, sedation is not a common adverse effect. Antimuscarinic side effects such as dry mouth, blurred vision, constipation, and retention of urine are also less likely with second-generation agents. However, elderly and those with benign hypertrophy of prostate may require caution due to the risk of urinary retention. Generally, second-generation agents are devoid of troublesome adverse effects.

8.3.3.3 Mast Cell Stabilizer

Mast cell stabilizers act by stabilizing the mast cell membrane and preventing release of histamine and slow-reacting substance of anaphylaxis (SRS-A). These agents bind with the calcium transporter on the surface of mast cells and inhibit binding of calcium with this transporter which is essential for the release of histamine and other mediators after antigen-antibody interaction. There may also be additional mechanisms of action of mast cell stabilizers such as phosphorylation of membrane proteins essential for degranulation and release of mediators.

Disodium cromoglycate was the first mast cell stabilizer used in clinical practice. It is not absorbed from gastrointestinal tract after oral administration and hence is administered topically as 4 % eyedrops. It is well distributed in the precorneal tear film and also penetrates the conjunctival epithelium and substantia propria. Systemic absorption following repeated instillation is negligible. Other mast cell stabilizers that are used in clinical practice include nedocromil sodium (2 %), lodoxamide (0.1 %), and pemirolast (0.1 %). Their mechanism of action is similar to disodium cromoglycate.

Since mast cell stabilizers inhibit the release of histamine even upon exposure of sensitized cells to antigens, they are primarily used for prophylaxis. Disodium cromoglycate 4 % requires administration of 1–2 drops four to six times daily. Lodoxamide (0.1 %) and pemirolast (0.1 %) are administered as 1–2 drops four times daily, whereas nedocromil sodium (2 %) is administered twice daily.

Systemic adverse effects of mast cell stabilizers are uncommon because they are not absorbed systemically. Headache, however, may occur especially with pemirolast. They may cause local adverse effects such as mild and transient irritation, redness, and ocular and periocular itching. Mast cell stabilizers are contraindicated in patients who are allergic to drug or any other constituent of the topical preparation.

8.3.3.4 Dual-Action Agents

Introduction of dual-action drugs was an important step forward in the treatment of ocular allergies. Since the dual-action drugs combine the histamine receptor-blocking and mast cell-stabilizing effects, they not only relieve the symptoms but can also prevent the further occurrence of allergic episodes. The drugs available from this class for topical use include azelastine 0.05 %, epinastine 0.05 %, ketotifen 0.025 %, and olopatadine 0.1 %. Among all, ketotifen is the only drug available as unit dose without preservatives and hence is most suitable for contact lens wearers, although olopatadine has also been successfully used to treat allergic conjunctivitis in contact lens wearers (Brodsky et al. 2003).

Emedastine and ketotifen were found to be equally effective in relieving itching (Verin et al. 2001; D'Arienzo et al. 2002) and the efficacy of both of them has been shown to outperform levocabastine (Kidd et al. 2003). Olopatadine was found to be more effective than azelastine for relief of itching (Spangler et al. 2001). However, when compared to ketotifen, olopatadine showed no significant differences (Avunduk et al. 2005) but patient preferences were found to be in favor of olopatadine due to convenience of dosing (Leonardi and Zafirakis 2004). When compared

with epinastine and levocabastine, olopatadine was found to have higher efficacy in relieving the redness and itching (Lanier et al. 2004; Abelson and Greiner 2004).

Headache, burning, and irritation are common side effects of dual-action drugs. They may also cause foreign body sensation, dry eyes and itching in and around the eyes. Systemic adverse effects are not seen with these drugs as the systemic absorption is minimal.

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