Review of Various Lacrimomimetics: Making The Appropriate Choice

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Abstract

Dry eye disease (DED) is a very common problem, and the incidence is progressively increasing. Lacrimomimetic (ocular lubricating or artificial tears) eye drops have traditionally been the first line of treatment of DED. They are also prescribed to treat related pathological conditions such as keratoconjunctivitis sicca (KCS) and other diseases of the ocular surface. Besides protecting the ocular surface, these medicines also promote epithelial regeneration. There are many lacrimomimetics available as over the counter (OTC) drugs and prescription drugs, which vary in their mechanism of action depending upon properties like electrolyte composition, osmolarity, and addition of preservatives. Knowledge of the properties of various lubricating agents and understanding the subtle differences among them will help in making the appropriate therapeutic choice.

Introduction

Dry eye disease (DED) is a relatively common condition affecting approximately 10% to 20% of the adult population. Globally, approximately one out of seven individuals aged 65 to 84 years reports symptoms of DED. It is also reported that the prevalence of DED gets double after the age of 59. The incidence of DED is progressively increasing with increase in environmental pollution and change in urban lifestyle with increased exposure to air-conditioners and digital screens (mobiles, laptops etc.).

DED is a multifactorial disease of the tears and ocular surface that causes symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is characterized by the degradation of the tear film and increased ocular inflammation. The tear film is composed of three distinct layers: an inner mucin layer that adheres to the corneal epithelium, the middle aqueous layer that forms the bulk of the tear film, and an outer, mostly lipid layer that interacts with the environment and prevents evaporation of the aqueous layer. These layers are produced by the meibomian glands, the lacrimal gland and goblet cells of the conjunctiva, respectively. The structural integrity of the tear film is maintained by the complex interaction between these layers. A variety of factors can disturb this interaction and degrade the tear film, such as systemic autoimmune diseases (e.g. Sjögren’s syndrome), dietary deficiencies, environmental factors (e.g. smoke, contact lenses), systemic conditions (e.g. Diabetes mellitus) and dysesthesia (after refractive surgery). The clinical symptoms of DED include pain, foreign body sensation, dryness or irritation, burning, light sensitivity, redness, and eyelash debris.

Additionally, eye inflammation can inadvertently lead to further dysfunction of the ocular surface, in turn leading to further tear reduction and inflammation. DED can be divided into tear deficient and evaporative types. Tear deficient DED can further be subdivided into non-Sjögren syndrome and Sjögren syndrome, which is an autoimmune disease associated with lacrimal and salivary gland lymphocytic infiltration. Evaporative DED can be divided into meibomian gland disease (MGD) and exposure-related DED.

Another group of patients, mucin deficiency due to Stevens-Johnson syndrome or ocular cicatricial pemphigoid is the underlying mechanism of DED. The primary and first line treatment for DED are lacrimomimetic eye drops, commonly known as artificial tears or ocular lubricating eye drops. Lacrimomimetics are synthetic ocular lubricants that supplement one or more components of the lacrimal film by increasing the tear volume and stability and by protecting the ocular surface against desiccation.

The active pharmaceutical ingredient (API) of most commonly prescribed lacrimomimetics are carboxymethylcellulose (CMC), hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG), propylene glycol (PPG) and sodium hyaluronate (SH). In immunological conditions such as keratoconjunctivitis sicca (KCS), immunomodulator agents along with steroids are the therapeutic choices which reduce the inflammation besides stimulating tear production.

Lacrimomimetics act just as an adjunct until normal tear production is restored. While the composition of lacrimomimetics must be similar to that of natural tears in order to simulate its organic characteristics, the full complexity of the lacrimal film cannot be reproduced yet. Consequently, the formulations of ocular lubricants are constantly being revised and updated. Given the variety of available products, the aim of this review is to present the main formulations of lacrimomimetics and their effect on the ocular surface, and thus guide clinicians on the best choice for each individual patient.

Development of Lacrimomimetics

An ideal lacrimomimetic must provide an environment compatible with the maintenance of the ocular physiology and must support epithelial healing. The key properties governing the pharmacokinetics and pharmacodynamics of lacrimomimetics are electrolyte composition, osmolarity, and presence of preservatives. A physiologically healthy lacrimal film is necessary for proper interaction between the structures of the ocular surface. Disorders of the ocular surface increase the friction of the eyelids over the cornea and conjunctiva, which can

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be minimized with the addition of lubricants or viscosity agents.\textsuperscript{8,16} Furthermore, the formulations of lacrimomimetics must accommodate the necessity of intermittent instillation, while aiming to mimic the continual production of natural tears.\textsuperscript{14} Thus, viscosity agents are included in the formulation in order to increase the contact time of the drop with the ocular surface and extend comfort duration.\textsuperscript{8} The disadvantages of such agents are transient blurring of vision and the accumulation in the eyelashes.\textsuperscript{8,17} 

The most commonly prescribed lacrimomimetics include:

1. **Cellulose derivatives**
   - a. Carboxymethylcellulose
   - b. Hydroxypropyl methylcellulose (HPMC)

2. **Sodium hyaluronate (SH)**

3. **Synthetic polymers**
   - a. Carbomer (polyacrylic acid)
     - i. Polyethylene glycol (PEG 400)
     - ii. Propylene glycol (PG)
     - iii. Hydroxypropyl guar (HPG)
   - b. Povidone (polyvinylpyrrolidone)

4. **Lipid ointments**
   - a. Petrolatum
   - b. Mineral oil
   - c. Lanolin
   - d. Castor oil

5. **Newer Strategies**
   - a. Liposomes
   - b. Cationic emulsions

1. **Cellulose derivatives:**

CMC has desirable mucoadhesive and viscoelastic properties and a high retention time on the ocular surface.\textsuperscript{8,18,19} It is an anionic cellulose polymer with a carboxylic group and its anionic characteristic may be beneficial in increasing the retentive time on the cornea.\textsuperscript{12} Its ability to stimulate cellular migration has been established in vitro and in animal models.\textsuperscript{19,20} CMC is available in several viscosities which correspond to the different molecular weights.\textsuperscript{12} CMC is usually used in concentrations of 0.25%, 0.5%, and 1% and with different molecular weights ranging from an equivalent of less than 5 to more than 1000 centipoise.\textsuperscript{8,21} Concentrations higher than 1% can cause blurring of vision and secretion of sticky material in humans, but provide a higher retention time on the ocular surface, and hence require fewer daily instillations.\textsuperscript{21}

HPMC is another viscoelastic polysaccharide with good retention properties. It is less viscous than CMC but is known to be a superior cohesive and has emollient properties.\textsuperscript{12} While it is commonly used, it has the disadvantage of encrusting the eyelids, which may mimic blepharitis.\textsuperscript{17}

2. **Sodium hyaluronate (SH)**

SH is a glycosaminoglycan disaccharide biopolymer and consists of repeating alternating sequences of N-acetylglucosamine and glucuronate in linear chains. It is a long molecule with a flexible, open-coil conformation.\textsuperscript{22} SH is present in natural tears, with excellent viscoelastic, lubricating and water retentive properties besides resisting evaporation. The water retentive property contributes to the stability of the tear film, and the wettability of the ocular surface.\textsuperscript{2} In addition, SH may not only “hold” water but also act as a reservoir of slowly releasing water molecules.\textsuperscript{12} SH also promotes epithelial cell migration, thereby supporting epithelial healing.\textsuperscript{8,14,24} SH has a direct role in ocular inflammation and in cellular adhesion and migration.\textsuperscript{14,24} SH has been shown to reduce the level of the inflammatory marker CD44, which is over expressed in DED.\textsuperscript{25} One study comparing CMC, HPMC and SH has shown that 0.3% SH has the highest ability to protect the corneal epithelial cells from desiccation and the effect is concentration dependent.\textsuperscript{12} However other studies have shown that CMC shows more improvement than SH in tear breakup time and corneal staining, thus is more efficacious in treating DED.\textsuperscript{26-28} Few studies have also revealed a greater reduction of inflammatory markers in the CMC group than in the HA group.\textsuperscript{26-28}

The combination of CMC and SH has high viscosity under low friction conditions (between blinking), thus stabilizing the tear film, but low viscosity under high friction conditions (during the blinking), thus it causes less adverse effects such as discomfort.\textsuperscript{30} The analysis comparing three formulations: CMC 0.5% and SH 0.1%, CMC 0.5% and SH 0.15%, and CMC 0.5% showed that the combination of CMC and SH was well tolerated and led to better treatment outcomes, causing less adverse effects when compared to one polymer alone.\textsuperscript{29}

3. **Synthetic polymers**

Synthetic polymeric lubricants that are commonly used are carbomer (polyacrylic acid) and povidone (polyvinylpyrrolidone). Carbomer is a polymer with a high viscosity and a good retention time, but it causes intense blurring.\textsuperscript{17} Povidones are linear polymers with mucinomimetic properties and have a good retention time.\textsuperscript{17} They are often added to cellulose-based solutions to supplement both the aqueous and mucin layers of the tear film or to polyvinyl alcohol solutions to increase wetting of the ocular surface.\textsuperscript{17} HPG is used in combination with PEG and PG as a gelling agent that adapts to the abnormalities of the lacrimal film and alterations on the ocular surface.\textsuperscript{30} An ophthalmic formulation of HPG includes sorbitol and borate. The formulation is stored at pH 7, at which sorbitol binds to borate. This promotes a low solution viscosity, which facilitates the instillation of the eye drops and decreases the immediate adverse effects. Once instilled in the eye, where the pH is around 7.5, this link is dissociated, and HPG binds to borate and forms a gel with bio adhesive properties, increasing the duration of exposure to the active ingredients.\textsuperscript{13,31} HPG molecules bind to the hydrophobic regions, i.e., areas where the glycosyl complex integrity is compromised, and promote local healing and lubrication.\textsuperscript{15} HPG solutions are an effective treatment for KCS as they increase the tear break up time (TBUT).\textsuperscript{32} A commercial solution of HPG has been shown to provide protection against desiccation in vivo (rabbit models) and in vitro, and...
provide a favorable environment for the regeneration of epithelial cells. Comparisons between PEG/PG and HPG with solutions of CMC 0.5% with glycerin and compatible solutes, CMC 1%, and glycerin 1% and polysorbate 80 1% have also demonstrated its superior efficacy. However, some studies reported that there is no difference between these formulations regarding the reduction of symptoms, patient satisfaction, and safety of the product.

4. Lipid ointments
Lipid ointments are used to supplement the lipid layer of the tear besides lubricating the ocular surface. Consequently, they increase the lacrimal stability and overcome the limitations of retention time that are seen in the aqueous agents. Lipid ointments are indicated in cases of severe evaporative KCS and meibomian gland dysfunction. The most commonly used lipid ointments are petrolatum and mineral oil. In some cases, lanolin is also used, but it can cause irritation and it retards regeneration of the corneal epithelium. Most lipid ointments do not require the use of preservatives, because bacterial growth is limited in these formulations.

Some recent reports have shown the beneficial properties of castor oil on the reestablishment of the tear lipid layer, and in the treatment of meibomian gland dysfunctions (MGD). The main component of the castor oil-based formulation is ricinoleic acid, an omega-9 unsaturated fatty acid that immediately spreads over the aqueous layer.

5. Newer strategies
New techniques have been developed in recent years to reduce the adverse effects. These include development of liposomes that contain phosphatidylcholine, cholesterol, Vitamin E, and SH to replace the aqueous-mucin layer and increase the retention time. The pH, osmolarity, viscosity, and surface tension of this solution are suitable for ophthalmic use and exhibited good tolerability in vitro and in vivo.

Recently, cationic emulsions have also been introduced in the formulation of ocular lubricants. Cationic emulsions contain positively charged lipid droplets that are attracted to the negatively charged ocular surface through electrostatic interactions, thus increasing retention time. The nano scale size of the droplets also amplifies their bioavailability. Compared to a synthetic polymer lubricant, the cationic emulsion has superior tear break up time and lissamine green stain results, indicating better integrity of the lacrimal film and protection of the ocular surface.

Properties of The Lacrimomimetics
Besides API, other factors governing the efficacy and safety profile of the lacrimomimetics are-

- Electrolytes
- pH
- Osmolarity
- Preservatives

The addition of electrolytes, mainly bicarbonate and potassium, to lacrimomimetics can be beneficial for the ocular surface. The correct electrolyte composition is essential to the maintenance of the goblet cell density and the corneal glycogen levels. There is also evidence that the presence of calcium improves ocular surface symptoms as it is required for intercellular adhesion.

Lacrimonimetics usually have a neutral to mildly alkaline pH. Solutions with a higher pH seem to increase ocular comfort. Sodium bicarbonate is frequently added to ophthalmic solutions as a buffer and provides a mildly alkaline pH. Bicarbonate also plays a role in regenerating the epithelial barrier and maintaining the corneal ultrastructure. Other buffers include proteins, phosphate, acetate, and borate.

In cases of DED, it has been well established that the osmotic pattern of the tear film is altered due to the high evaporation rate and the reduced aqueous flow, which results in hyperosmolarity, above 316 mOsmL⁻¹. Increased osmotic stress leads to oxidative damage and the activation of inflammatory cascades, which culminates in the death of goblet cells. Loss of goblet cells leads to alterations of the mucin layer, and hence further instability of the tear film. This creates a vicious cycle that is central to the pathophysiology of the disease. Thus, although many lacrimomimetics are isotonic, some have low osmolarity, with the aim of diluting the diseased tear film back to normal osmolarity.

While some studies have indicated that hypotonic solutions are superior regarding the improvement of symptoms and patient compliance, others failed to find significant differences between isotonic and hypotonic solutions.

The addition of osmoprotectants has been reported to neutralize the damage caused by hyperosmolarity in patients with KCS. The proposed mechanisms of action are antioxidant action, stabilization of protein surfaces, and restoration of cellular volume. Osmoprotectants commonly used in artificial tears are erythritol, glycerol, L-carnitin and betaine. L-carnitin and erythritol protect the corneal cells against osmotic stress. Betaine suppresses the expression, production, and activation of metalloproteinases. Metalloproteinases are enzymes responsible for tissue remodeling. However, in a hyperosmotic environment, their production is increased and can lead to corneal ulcers and corneal melting. Thus, the control of metalloproteinase expression is desirable.

Preservatives are added to the formulations to prevent contamination in the bottle, which may cause severe ocular infections. However, these substances are highly toxic to the ocular surface when chronically used, and may worsen the inflammation and disease. While this toxicity is dose-dependent, even the low concentrations reported in commercial products can cause deleterious effects.

Major categories of preservatives are-

1. Detergents
   a. Benzalkonium chloride (BAK)
   b. Cetrimide
   c. Polyquad
2. Oxidative agents
   a. Sodium perborate
   b. Stabilized oxychloro complex (SOC)

BAK has been the most frequently used preservative in the last few decades and is extremely toxic to the conjunctival and corneal cells. When chronically used, it destabilizes the tear film, and affects the intercellular junctions, the cellular morphology, and the microvilli. It also reduces the goblet cell density, thus altering the mucin layer, and can eventually cause apoptosis or necrosis and epithelial desquamation. Toxicity is dependent on concentration, frequency of administration, severity of the ocular disease and the level of lacrimal secretion. Therefore, the deleterious effects are worse in KCS patients due to the high exposure of corneal epithelium and the low volume of tears to dilute the drug. In addition, there is evidence that BAK can affect the trabecular meshwork.

A clinical trial comparing preservative-free formulations demonstrated that the preservative-free treatment leads to significant improvement on the Schirmer’s test, TBUT and impression cytology compared to solutions containing BAK. Furthermore, the preservative can interfere with the anti-oxidative and anti-inflammatory responses on the ocular surface. Polycationic quaternary ammonium compounds (Polyquad) is a quaternary ammonium compound. Although it is a detergent similar to BAK, its toxicity is restricted due to its high molecular weight, which limits epithelial cell penetration, thereby reducing the damage to the lacrimal film and ocular surface.

Oxidative preservatives, such as sodium perborate and SOC, have antibacterial action and minimal toxicity. Sodium perborate dissolves in water and releases hydrogen peroxide, which when in contact with the ocular surface is in turn converted into water, chlorine and oxygen (natural tear components). However, hydrogen peroxide, even at low concentrations, may injure the ocular surface. SOC is a mixture of oxychloro species (chlorite 99.5%, chlorate 0.5% and traces of chlorine dioxide) that have antibacterial, anti-fungi and anti-viral action. The mechanism of action is the release of chlorine dioxide in acidic microbial environments, and the interference with microbial protein synthesis. When in contact with the lacrimal film, it is converted into natural tear components such as water, oxygen, sodium, and chlorine. This preservative has mild cytotoxic effects, good tolerance, and an excellent safety record. Although SOC has been shown to cause superficial punctate corneal fluorescein staining, it had considerably minor deleterious effects.

The toxic effects of the preservatives are determined by their concentration, retention time, and frequency of administration. Therefore, they are considered safe when applied less than six times a day. When frequent instillation is necessary or the tear flow is reduced, a preservative-free solution is recommended.

Formulation Choice

The choice of which eye drop to prescribe must take into account factors such as cost, packaging, availability, clinician preferences, type and severity of the lacrimal abnormality and patient response.

For quantitative abnormalities of the aqueous layer, viscous eyedrops are recommended, where the viscosity is dependent on the severity of the disease. For qualitative abnormalities, ointments or mucinomimetics are recommended. In addition, due to the high retention time, ointments are recommended for treating severe cases. In DED, the recommended frequency of application is four to six times daily. Ointments may be prescribed to reduce the number of applications to once or twice daily depending upon the severity of DED.

An algorithm has been developed that guides the choice of lacrimomimetics for patients. The first choice should be CMC, HPMC or SH based eye drops. If the improvement is not as expected after instilling the eye drops four times a day for 60 days, the eye drops should be exchanged for a HPG or PEG/Glycerin-based eye drop. If the response is still not as expected or when the condition is severe, or in cases of exposure keratopathy or lid malposition, the choice should be to add gels, ointments, or liposome sprays. Choosing a preservative-free eye drop, regardless of lubricant component, should be the priority to avoid exacerbating the condition.

An important limitation in the literature is that most studies have been single center comparisons between two or three formulations. The literature lacks a broad, randomized, multicenter study that compares a large variety of solutions. However, a better understanding of pathophysiology of DED and the mechanism of action of various lacrimomimetics may help the clinician to choose the most appropriate medicine for a particular patient.

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