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Dry Eye Syndrome

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ABSTRACT

Use of video display terminals (VDTs) is associated with a decreased frequency of blinking and an increased rate of tear evaporation. This leads to ocular fatigue (1), which is one of the major symptoms of dry eye (2). The causes or alterations in the normal tear film that lead to dry eye syndrome or keratoconjunctivitis sicca are given here, followed by a brief account of the diagnostic measures. Various compounds and dosage forms that are in use and emerging for the treatment of dry eye are described.

INTRODUCTION

The terms *dry eye* and *keratoconjunctivitis sicca* (KCS) are most commonly used to indicate problems of the ocular surface connected with reduction or instability of the percorneal tear film. A brief description of normal tear film follows.

THE PRECORNEAL TEAR FILM

In recent years the precorneal tear film has been a subject of great interest. It consists of three layers: an anterior thin lipid layer, a thicker aqueous layer, and a thin mucoid layer covering the corneal epithelium (3).

- *Anterior layer*: The mebomian glands of the eyelids secrete an oily substance which allows the corneal surface to be wetted (4). It smooths the tear film and makes the eyelid margin hydrophobic (5,6). These lipids reduce evaporation of tears (5–7).
- *Middle layer*: The aqueous layer, supplied by the main and accessory lacrimal glands, constitutes about 98% of this trilaminar film. This layer is composed mainly of water, electrolytes, and various proteins. The proteins lower the surface tension of tears and help to spread them (8,9). The osmotic pressure of the tear film is around 311 mOsm in normal eyes. The normal pH of tears is 6.5–7.6. The turnover of tears is heavily dependent on environmental conditions, such as temperature, relative humidity, and wind as well as age and the physiological state of the patient (7). The cul-de-sac normally holds 7–9 μL of tears but

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can retain upto 20–30 μL without overflowing if care is taken not to blink.

- *Posterior layer*: The posterior layer of the tear film is a mucin layer secreted by the goblet cells located on the conjunctival surface. Mucus is a mixture of neutral and acidic mucopolysaccharides. It contributes stability to the tear film (7). The role of the mucus in wetting the corneal surface offers a possible explanation of a variety of clinical observations, for example, the formation of dry spots and eventually the extensive nonwetting seen in dry conditions with mucus deficiency, such as vitamin A xerosis and ocular pemphigoid.

PATHOPHYSIOLOGY

The even distribution of tears on the surface of the eye and the ability of various components of the tear film to maintain the normal tear structure are determined by an adequate volume and quality of secretion (10), and by the frequency and completeness of blinking. When any of these factors is impaired, the tear film is disrupted. Persistent disruption of tear film often leads to symptoms characteristic of KCS (11). It develops slowly and insidiously (12) as a conjunctivitis with a mild degree of conjunctival infection associated with a considerable amount of irritation, photophobia, foreign-body sensation (13), and burning. Systemic symptoms like nasal dryness, dry mouth, recurrent bronchitis, constipation, joint pain, eczema, etc., may be associated with dry eye. The underlying causes of dry eye can be:

1. Aqueous tear deficiency
2. Mucin deficiency
3. Lipid abnormalities or
4. Impaired lid function

In subjects with KCS, tear production is decreased (14). Due to increased evaporation rate (15), tear film osmolarity is increased (16,17). Altered tear evaporation can thus be a cause and a result of dry eye.

Decreased goblet cell density leading to mucin deficiency is an important pathologic change in KCS both in humans (18–20) and in rabbit models (21,22). Goblet cell dysfunction is usually due to vitamin A deficiency.

Mebomian gland dysfunction (MGD) has been believed to be one of the major causes of ocular discomfort and abnormalities of the ocular surface (23). Tear deficiency may or may not be accompanied with the disorder. An excessive evaporation of tears may have been responsible for the changes that are observed.

Compromise of normal lid–globe contact or an abnormality in the blinking process can adversely affect mucus distribution and turnover. Ocular surface area and blink rate affect tear dynamics (24). Not only total tear evaporation, but also evaporation per unit area increases with the exposed ocular surface. This increase in evaporation per unit area can be attributed to the thining of the mucin and lipid layers of the tear film as they spread over a larger area (25,26).

Use of VDTs, widely employed in modern technology, is associated with a decreased frequency of blinking and an increased rate of tear evaporation (1). This leads to ocular fatigue, which is one of the major symptoms of dry eye (2).

Some systemic medications may also lead to decreased lacrimal secretion (13). Examples are: a few antihistaminics, beta blockers, diuretics, methyldopa, anticholinergics, opiates, atropine, scopolamine, and psychotropics like benzodiazepines, monoamine oxidase (MAO) inhibitors, phenothiazines, and tricyclic antidepressants.

ANIMAL MODELS

Experimental KCS can be produced in rabbits either by closing the lacrimal gland excretory duct only or by, in addition, removing the nictitating membrane and harderian gland (21). A murine model of Sjogren's syndrome with lacrimal gland inflammation is developed in autoimmune mice (27).

DIAGNOSIS

Investigation of KCS is presented here under following headings: physical examination, clinical diagnostic tests, and laboratory tests.

Physical Examination

Normally tear meniscus height is 0.2 to 0.3 mm. In dry eyes it is decreased. Short filaments and mucus strands are often present in the tear film.

Clinical tests

1. Rose bengal stain: 1% rose bengal solution stains devitalized cells and mucus (28,29).

2. Fluorescein stain (30): The staining of the inferior third of the cornea is an indicator of more severe tear film malfunction.
3. Tear film breakup time (TBUT): This reflects the relative stability of the tear film. It is defined as the interval between complete blink and the appearance of first randomly distributed dry spot on the corneal surface. The test reflects the integrity and functionality of the mucus layer of the tear film. The average TBUT is 25–30 sec. A TBUT under 10 sec can be considered abnormal in the presence of adequate tear production (31). This can be due to mucus deficiency or lipid abnormality.
4. Schirmer test (32): Schirmer-1-test describes insertion of strips of blotting paper into the lower conjunctival fornix and measuring the length of the tear-wetted part after exactly 5 min. A value of less than 5 mm indicates impaired secretion. Most normals will wet between 10 and 30 mm. Since this test stimulates some reflex tearing, Schirmer's test with anesthesia is used, which is capable of measuring a basic tear secretion independent of reflex component (33–36). One study (37) correlates the length of wetting to the weight of tear fluid absorbed in the paper strips. A linear relationship is demonstrated. When obvious clinical signs are not present, Schirmer's test is the only practical, objective clinical test available to most clinicians (38) to help support the diagnosis.

Laboratory Tests

1. Lysozyme measurement: The tear lysozyme concentration is found to be decreased in KCS. The agar diffusion technique is described as a routine clinical procedure (39). *M. lysodeikticus* is used as a substrate. Filter paper disks entirely wetted with tears are incubated on the medium. The diameter of lysis is measured.
2. Goblet cell count/conjunctival biopsy: This can be helpful in confirming the diagnosis of mucus deficiency.
3. Tear osmolarity: In dry eye it is greater than 312 mOsm/L.
4. Tear mucin measurement is done by measuring the hexosamine content (30).

To evaluate tear dynamics more efficiently, Xu (40) developed the concept of Tear Function Index, which combines values of both tear secretion and drainage tests.

Lemp (41) has provided a guideline for grading dry eyes. It is a latin square diagram, four sides of which are scores of four tests, namely, rose bengal staining. TBUT, tear osmolarity, and Schirmer wetting time. Total area of the square is divided into three different grades of dry eye. Accordingly, treatment modalities are also suggested.

TREATMENT AND PHARMACEUTICAL ASPECTS

Ideally the ingredients of artificial tear formulations should fulfill the physicochemical role of a normal tear. This implies compatibility with the natural components of tears and no alteration in the clarity of the aqueous layer. An effective tear substitute should lower the surface tension of the tear film, aid the formation of a hydrophilic layer that is compatible with adsorbed mucin, and enhance tear volume when necessary (42). In the absence of functional mucin, it should be able to form a hydrophilic layer and exhibit the functional properties of a normal mucin layer (43). Preferably the topical application of artificial tears should manage aqueous- and mucin-deficient dry eyes. If it thickens the tear film, it may also help in correcting minor epitheliopathies (43,44). The mainstay of treatment of dry eye conditions remains the supplementation of tear production by artificial preparations.

Artificial Tear Solutions

Though instillation of normal saline is capable of giving comfort, it is of very limited value because it is not retained in the conjunctival sac for more than a few minutes. So additives were developed and used initially to thicken the tear substitutes; these were believed to prolong their action. Lubricants formulated as solutions consist of inorganic electrolytes to achieve tonicity and maintain pH, preservatives to prevent bacterial growth, and water-soluble polymeric systems. The polymers can alter the viscosity of the solution and decrease the wetting angle of saline solution on a mucin-free but polymer-coated cornea in vitro (42). Examples of the early polymeric ingredients are substituted cellulose ethers such as methylcellulose (MC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), and carboxymethylcellulose (CMC) (43). These colloids dissolve in water to produce

solutions of varying viscosities. They have the proper optical clarity and a refractive index similar to cornea, and they are nearly inert chemically (45,46). Cellulose ethers are compatible with many drugs and chemicals used for the eye. Besides prolonging ocular retention time by enhanced viscosity, these polymers may adsorb at the cornea–aqueous tear layer interface, thereby stabilizing a thicker layer of fluid adjacent to the adsorbing surface (44,47,48). Increased TBUT found with these compounds is consistent with this assumption (49,50). Polyvinyl pyrrolidone (PVP) appears to be capable of forming hydrophilic coatings in the form of adsorbed layers (51). Polyacrylic acids or carbopol resins, which have greater pseudoplasticity and bioadhesion, are also used to stabilize the tear film (52).

Preservative-Free Preparations

The problem with current ophthalmic preservatives lies not with their efficacy as antimicrobials, but rather with their recognized cytotoxic side effects on the corneal epithelium (53–56). Preservatives have been shown to disrupt the precorneal tear film and damage the epithelial surface (57,58). KCS may be aggravated by frequent use of preservative containing aqueous tear preparations (56). Hence for frequent dosing, preservative-free preparations are suggested. Bicarbonate is recommended for such formulations (59). Formulations should be adjusted to a neutral pH and a safe osmolarity range (60) in order to minimize toxicity.

Vitamin A Derivatives

Vitamin A is provided to the corneal epithelium by tears (61) so a deficiency is expected in certain cases of dry eye, especially Sjogren's syndrome. Promising results are reported with Retinol, 500 IU/mL tears (62). Topical use of both Tretinoin (all-trans retinoic acid) and Retinol, the alcohol form of Vitamin A, is also reported (63–67). The therapeutic efficacy has been attributed to the restoration of cellular differentiation, with goblet cell regeneration and enhanced mucin production, whereby the interactions between epithelial cell surface and tear film are normalized (67).

Viscoelastic Agents

Sodium Hyaluronate

A polysaccharide polymer (glycosaminoglycan), hyaluronate is present in the vitreous and aqueous humour of the eye. At physiological pH, it is a viscoelastic solution (42). A variety of dry eye syndromes show improvement with hyaluronate treatment. Viscoelastic properties which lubricate as well as protect the ocular surface account for the beneficial effects (68). Hyaluronic acid seems to be beneficial not only as a mucin substitute but also as a fibronectin inducer in dry eye management. It is nonantigenic and does not cause inflammatory or foreign-body reaction (69).

Chondroitin Sulfate

A polysaccharide of D-glucuronic acid and *N*-acetyl galactosamine, chondroitin sulphate is 350,000 times as viscous as saline. It is reported to be uniformly preferred by patients (70). It is a Newtonian fluid that has a constant viscosity even with low shear rates.

Mucolytic Agents

An *N*-acetyl derivative of the naturally occurring amino acid L-cysteine, acetyl cysteine has been useful as a mucolytic agent (71); it acts to open up disulfide linkages in mucus, thereby lowering its viscosity (72). A greater objective improvement in signs such as conjunctival and corneal staining, mucus threads, and filaments by slit lamp examination is observed (73) in KCS patients using acetyl cysteine solution.

Tear-Stimulating Agent

Lacrimomimetic agents, such as bromhexine, have been widely used in some countries, both topically and systemically (41). Bromhexine stimulated tear secretion significantly (74,75).

Bland Ointment Formulations

Both mucin- and aqueous-deficient dry eyes may benefit from the application of lubricating ointments. This provides lubrication during the night without substantially blurring the vision the following morning (41). The ointments are semisolid preparations of petrolatum and mineral oil to which lanolin may be added. Ointments are retained longer in the tear fluid because of their molecular size, better adsorption to the cornea, and entrapment by mucus (76).

Lipid Preparations

These are especially suitable for MGD dry eye. Myristyl alcohol, myristyl lactate, lauric acid, choles-

terol, linoleic acid, cocamide derivative, and phospholipids are used (77,78).

Artificial Tear Inserts

This is a more recent approach for moderate to severe dry eye syndromes. These are water-soluble polymeric rods that provide constant release of polymer over a period of hours, when placed in the inferior cul-de-sac (76,79,80). The artificial tear insert Lacrisert® is a cylindrical rod of 5 mg of HPC without preservative. These inserts require some degree of hydration to work and in patients with severe conditions, the inserts must be used in conjunction with other artificial tears to initiate the dissolving process (41). This treatment provides a clinically thicker tear film than normal, which retains fluid within it (81,82). The device is generally comfortable and well accepted. It has some disadvantages, however, such as the dexterity required to properly place the insert into the lower cul-de-sac, blurred vision sometimes associated with intense release of polymer for a few hours following instillation, and the high cost.

Contact Lenses

Bandage-soft contact lenses provide a moist covering and exchange some of their fluid with the epithelium (83), thus playing a role in rehydrating desicated epithelium. These lenses must be used in conjunction with artificial tears as they tend to dry out quickly. Moist glasses or spectacles with side panels are also reported to give greater comfort and improvement (84).

Punctal Plugs

Punctal occlusion can benefit patients whose symptoms of dryness and other ocular abnormalities are not relieved by topical therapy alone (85,86). A silicone plug (Freeman plug) has been developed that can be inserted into the inferior and superior puncta after punctal dilation. Permanent punctal occlusion usually involves the application of heat to the puncta to effect a permanent seal (41).

Other Therapies

Some of the newer therapies proposed are anti-inflammatory therapy of cyclosporine A (87,88), interferon-alpha treatment in certain types (89), and RGD peptides (62). Steroid therapy has been in use for decades in the management of some cases of dry eye (41,90).

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