Drugs used in the treatment of dry eye syndrome, anti-inflammatory drugs and topical anti-allergy drugs

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This article will cover the factors causing dry eye syndrome and the drugs, both topical and systemic, used in its treatment. Also the effectiveness and limitations of topical corticosteroids, non-steroidal anti-inflammatory drugs, mast cell stabilisers and antihistamines.

Drugs used in the diagnosis and treatment of dry eye syndrome

Tear production

The tear film normally consists of three layers:

1. A thin outer lipid layer
2. A thick middle aqueous layer
3. An innermost mucin layer[1].

Although at one time, tears were conceived as a discreet three layered structure, recent research suggest that these layers interact forming complex structures. Some experts believe that in dry eye there is a hyperosmolarity of tears, which activates the T-lymphocytes and production of inflammatory cytokines. Current understanding of the pathogenesis of dry eye disease has proceeded from recognition of a lack of, or altered quality of tears, to recognition of inflammation as the key pathogenic mechanism whether from a systemic autoimmune disease or a local autoimmune event. Often a negative feedback loop is set up where inflammation produces epithelial damage, producing further secretion of inflammatory mediators, which produces more damage[2,3,4,5].

Tear secretions are subject to parasympathetic, sympathetic, hormonal (androgen) and emotional regulation. Hormonal factors are important in Non-Sjögren's associated keratoconjunctivitis sicca (KCS) as it is often associated with post-menopausal women. One explanation is that the lack of androgens disrupts the function of the meibomian glands leading to a loss of (or a reduction in) the outer lipid layer in tears causing an increased evaporation of tears. The decrease in androgens is also thought to allow the accumulation of lymphocytes in the lachrymal tissue and increased secretion of pro-inflammatory cytokines, which contributes to dry eye conditions[1,3].

Cause of dry eye disease[1-6]

This can be caused by lack of tear production (eg vitamin A deficiency, drugs, Sjögren's syndrome), evaporation loss (eg blepharitis) and abnormalities in the mucin or lipid components of the tear film which impairs the spreading of the tears (eg alkaline burns, Stevens-Johnson syndrome and cicatricial pemphigoid). Blepharitis affects the meibomian gland and reduces the outer lipid layer allowing increased evaporation.

Drugs aggravating dry eye conditions

These include drugs possessing an anticholinergic action eg anti-Parkinsonism drugs, (benzhexol, orphenadrine), antihistamines, tricyclic anti-depressants, phenothiazines, anti-arrhythmics, diuretics, retinoids, beta-blockers, oral contraceptives and benzalkonium chloride.

Treatment

The aims of treatment are to relieve the symptoms of dry eyes and to restore, prevent, or minimise structural damage to the ocular surface. Obviously any treatment should be accompanied by life style changes eg avoid dry smoky atmospheres etc. to maximise the effectiveness of the treatment.

Treat underlying conditions – Blepharitis

Anterior/posterior blepharitis should

be treated by applying a warm flannel or pads to warm the eyelid gland secretions and to promote evacuation of the oil. Good lid hygiene will also remove crusting and clean the gland orifices. This can be done with warm water alone, although most practitioners recommend adding a few drops of baby shampoo. Topical fusidic acid is commonly used if required but in refractory cases oral tetracyclines (if no contra-indications) may be necessary for one to two months.

Artificial tears

The mainstay of treatment is replacement by artificial tears (table 1). They produce comfort but are also thought to reduce ocular inflammation by lessening tear osmolarity and flushing out inflammatory and other noxious agents. Patients are encouraged to use when necessary, and, if possible, reduce the number of drops to one drop four times a day.

Most multi-dose products have preservatives to prevent microbial contamination and the most commonly one used is benzalkonium chloride (BAK). Long-term use of BAK causes damage to the epithelial surface and decreases tolerability due to irritation. It can exacerbate ocular inflammation and induce tear film instability[4].

As an alternative to BAK oxidate transient preservatives were developed which dissipate upon contact with the eye reducing the risk of ocular surface damage. Examples of these are GenAqua (Novartis) and Purite (Allergan) which are found in products classed as devices rather than licensed as medicines. However, even these preservatives can cause mild irritation[4].

To reduce the problems caused by BAK, the consensus is that any artificial tears used more than six times a day should be preservative-free. Preservative-free products are usually expensive as they are in unit dose packaging and may be difficult to manipulate. A dispensing system has been produced (used in Hycosan) that allows a multi-dose preservative-free product. The mechanism for the dispensing system protects the preservative free artificial tear formula from contamination eliminating the need for the addition of preservatives[4,7]. Vismed multi is also a preservative-free multi-dose system.

There does not appear to be much difference between the various types of artificial tears with the main differences being the presence or absence of preservatives and the viscosity. Products with low viscosity are less likely to impair vision eg blurring, but are retained for a much shorter period of time in the eye. Hypromellose and polyvinyl alcohol have low retention time with the latter a longer retention time than hypromellose. More viscous products eg carbomers remain in the eye longer but can cause blurring of vision. Sufferers with more severe symptoms are willing to trade the increased blurred vision of the more viscous products for the increased comfort[4].

Gels and ointments, which are more viscous, tend to be reserved for night-time use or for the more serious dry eye conditions. In preserved products, an increase in viscosity increases the contact time between the preservative and the ocular surface and this possible adverse effect must be balanced against the increased duration of action of product[4].

Name	Brand name	Size	Cost NHS (£)
Hypromellose 0.3%		10mls	1.81
Hypromellose 0.5%	Isopoto Plain	10mls	0.85
Hypromellose 1%	Isopto Alkaline	10mls	0.99
Hypromellose and Dextran 70	Tears Naturale	15mls	1.68
Polyvinyl alcohol 1.4%	Liquifilm	15mls	1.93
Polyvinyl alcohol 1.4%	Sno tears	10mls	1.06
Carbomer 980 0.2%	Gel tears	10g	2.80
Carbomer 980 0.2%	Viscotears	10g	3.12
Carbomer 980 0.2%	Liposic	10g	2.96
Preservative free			
Hydroxyethylcellulose PF	Minims	30 units	5.75
Hypromellose 0.32%	Artelac SDU	30 units	8.71
Carbomer 980	Viscotears	30 units	5.75
Polyvinyl alcohol 1.4%	Liquifilm	30 units	5.35
Povidone 5%	Oculotect	20 units	3.40
Carmellose 0.5%	Celluvisc	30,60 units	5.75, 10.99
Carmellose 0.5%	Celluvisc	30,90 units	5.75, 15.53

Table 1
Net cost of lubricant eye drops licensed as medicines available in the UK. BNF 53rd edition[8]

Sodium Hyaluronate (Hyaluronic acid)

Sodium hyaluronate is a linear polymer composed of long chains of repeating disaccharide units of N-acetylglucosamine and glucuronic acid. It is a naturally occurring substance found in connective tissue and in synovial fluid. In the eye, it is found in the vitreous and in the aqueous humour at a lower concentration. It is also a natural component of tears[9].

Although there are several products on the market they are all classified as devices with a CE mark and are not prescribable by GPs (table 2). Therefore, patients must obtain their supplies from hospitals which are under pressure to cut their drug expenditure or purchase these products themselves.

In one trial using long-term hyaluronidate treatment, an improved cytology score was seen after three months. How hyaluronidate improves the ocular surface is currently unknown but several mechanisms have been advocated. Hyaluronidate is a natural polymer and its concentration increases in response to ocular damage. It can stabilise the ocular surface epithelial barrier and the suggestion is that it may be directly involved in the process of epithelial repair. Hyaluronate may play a part in controlling the localised inflammation often present in patients with keratoconjuctivitis sicca. Hyaluronate also increases the stability of the precorneal tear film, due to its water retentive properties, which improve ocular surface wettability. Finally, hyaluronate has viscoelastic properties that can lubricate the ocular surface reducing friction during blinking and ocular movements[10].

In one small trial, sodium hyaluronate 0.1% has been found to be more effective than 1.4% polyvinyl alcohol. There was a significant decrease in symptoms of burning and stinging and a significant lower Rose bengal staining. It was also found to be safe and well tolerated[11].

One concern has been raised concerning sodium hyaluronate products containing high phosphate concentrations. In the *British Journal of Ophthalmology*, there has been a report of five cases of deep calcium deposition in the cornea associated with ocular surface disease and frequent use of hyaluronic acid artificial tears. All patients used one formulation of phosphate buffered hyaluronate eye drops (found in Hylo-Comod and Hycosan) when rapid calcification developed[18].

The phosphate concentration in this formulation was measured and found to be much higher than other products. (50.9 mmol/l. compared to <0.1 mmol/l to 10.9 mmol/l.) The authors concluded that the hyaluronate artificial tear formulation favours the formation of insoluble crystalline calcium phosphate deposits in presence of epithelial keratopathy due to the high phosphate concentration in the product. Although, the patients used the product significantly much more frequently than recommended by

Name of product	% sodium hyaluronidate	Name of manufacturer	Preservative system
Aquify comfort drops	5%	CIBA Vision	Multidose use. Preservative system turns into oxygen and water on contact with the eye[12].
Blink	0.15%	AMO	Multidose use. Contains OcuPure which breaks down on contact with the eye to sodium chloride and water[13].
Hyal-drop	0.2%	Bausch & Lomb	Unit dose product. Preservative free.
Hycosan	0.1%	Bausch & Lomb	Multidose-preservative free. One way delivery system that prevents contamination of the drops. Manufacturers give product 12-week shelf life once opened.
Oxyal	0.15%	Kestrel	Multidose use. Contains Oxyd, which turns into oxygen, sodium chloride and water when in contact with the eye[15].
Vismed	0.18%	TRB CHEMEDICA AC. Distributed by Cantor & Nissel in UK.	Unit dose product. Preservative free[16]
Vismed	0.8%	TRB CHEMEDICA AC. Distributed by Cantor & Nissel in UK.	Unit dose product. Preservative free[17]

Table 2
A selection of sodium hyaluronidate "devices" available

the manufacturer, the manufacturers now state that Hycosan has been reformulated and is now phosphate free.

Acetylcysteine

Acetylcysteine is a derivative of the amino acid L- cysteine. It is commercially available as a 5% solution in 0.35% hypromellose (Ilube). It decreases the viscosity and tenacity of mucus and this liquefying action is due to the presence of a free sulphydryl group, which opens up disulphide bonds present in mucus. It is useful in patients who have sticky viscous mucus on the eye (filamentary keratitis). Other strengths 10% and 20% are available from specialist manufacturers. However, strengths greater than 5% do sting on application. Ilube can be sold, supplied or administered by additional supply optometrists[19].

Topical Ciclosporin

Ciclosporin is a fungal derived peptide. It prevents activation and nuclear translocation of cytoplasmic transcription factors, which are required for cell activation and inflammatory cytokine production. In clinical trials, topical application has been reported to increase aqueous tear production and decrease ocular symptoms. It has also been reported as healing corneal ulcers associated with Sjögren's syndrome[20]. Ciclosporin should not be used if the patient has an active infection or a history of herpes. It can cause some burning when applied to the eye.

In the UK, topical ciclosporin 0.2% ointment (Optimmune) is a veterinary product licensed for the treatment of canine keratoconjunctivitis. As it is an unlicensed product in humans, doctors prescribing it must take full responsibility, obtained informed consent and counsel patients well explaining why it is labelled for animal use only[21]. Ciclosporin eye drops 1% are available from Moorfields Eye Hospital as a 'special'. A ciclosporin 0.05% eye drop emulsion (Restasis), has been approved by the Food and Drug Administration (FDA) but it is not commercially available in the UK. Restasis comes in unit dose packages and is instilled night and morning[22].

In a multicentre randomised trial, topically applied ciclosporin A 0.05% was reported to produce significant improvement in the signs and symptoms of dry eye disease in patients with aqueous deficiency and keratoconjunctivitis sicca. Other studies show a significant decrease in the levels of both inflammatory cells and markers in the conjunctival epithelium and an increase in the number of goblet cells[2].

Autologous serum eye drops

These are prepared by the National Blood Service from the patient's own serum. Unfortunately, a positive serology for hepatitis B and C, syphilis and HIV excludes patients from this treatment. The patient donates approximately one pint of blood and the serum is extracted and diluted with saline, decanted into eye drop bottles and is frozen. Approximately 150 bottles are produced from each pint of blood and the process takes approximately six weeks. The patient needs to keep the stock frozen but one bottle should be allowed to thaw daily at room temperature. Once defrosted this bottle should be kept in the fridge and discarded at the end of the day[23].

There is no standard concentration agreed with some centres using 20%, some 50% and other neat autologous serum. More research on the optimum strength and dose is required (usually four to six times a day) plus data on long-term use.

The exact components in autologous serum eye drops that produce the beneficial effect have not been identified. Several tear factors have been identified to be of importance in the maintenance of normal corneal and conjunctival epithelium. These include epidermal growth factor (EGF), which accelerates corneal epithelial proliferation, Vitamin A, which if deficient in tears may lead to epithelial metaplasia and transforming growth factor ß (TGF-ß), which controls epithelial proliferation. All these factors are found in serum, although at a different concentration to tears[24].

The obvious disadvantage is that patients need to donate blood 3-4 times a year and if they are medically unfit to do so are excluded from this treatment. There appears to be few side effects or complications reported with the main problems being anaemia, risk of infection as the eye drops are unpreserved, and protein deposits on the eye (reversible on stopping the product)[23].

Topical steroids

Topical steroids improve both the signs and symptoms of dry eye in patients with moderate to severe dry eye who continue to have symptoms despite treatment or have evidence of corneal disease. Short two-week courses have been used to treat exacerbation of inflammatory symptoms. However, their use is limited by the side effect profile (see later).

Other drug treatments

Parasympathetic agents

Pilocarpine (Salagen) oral tablets can increase secretions via stimulation of the parasympathetic nervous system. It is licensed for the treatment of xerostomia and dry eyes in Sjgören's syndrome.

The recommended dose is 5mg four times a day with meals and bedtime. If tolerated but the response is insufficient, the dose can be increased to 30mg a day in divided doses. It is contra-indicated in uncontrolled asthmatics and obstructive pulmonary disease.

Also iritis and any eye disease where miosis is undesirable. Care should be taken in patients with cardiac disease as it can cause palpitations.

Side effects include those associated with excessive parasympathetic stimulation, such as increased sweating, increased urinary frequency, gastrointestinal disturbances including diarrhoea, flu-like symptoms and headaches. In clinical trials, pilocarpine has been found to be more effective in resolving dry mouth rather than dry eyes[6,8].

Bromhexine

Bromhexine is a secretolytic that increases the production of serous mucus. One trial on patients with Sjögren's syndrome (dose 48 mg/day)

Drug	Brand name	Presentation	Licensed indications
Diclofenac 0.1%	Voltarol Ophtha multidose	5ml	Inhibition of preoperative miosis during cataract surgery. Treatment of post-operative inflammation in cataract surgery. Control of ocular pain and discomfort associated with corneal epithelial defects after excimer PRK surgery or accidental non-penetrating trauma.
Diclofenac 0.1%	Voltarol Ophtha	Packs of 5 and 40 unit doses	Control of inflammation after Argon Laser Trabeculoplasty (ALT). The relief of the ocular signs and symptoms of seasonal allergic conjunctivitis (SAC). Treatment of inflammation and discomfort after strabismus surgery. Treatment of ocular pain and discomfort after radial keratotomy.
Flurbiprofen	Ocufen	40 x 0.4mls	The inhibition of intraoperative miosis. The management of post-operative and post-laser trabeculoplasty inflammation in the anterior segment of the eye in patients in whom steroid therapy is not recommended.
Ketorolac	Acular	5ml	Prophylaxis and reduction of inflammation and associated symptoms following ocular surgery. Contra-indicated in children.

Table 3
Licensed indications of topical anti-inflammatory drugs used in ophthalmology

reported that the values on the Schirmer test were significantly higher after bromhexine than after placebo. Also the break-up time was increased after bromhexine, which suggests that the drug has a dose-dependent effect on lachrymal gland secretion in Sjögren's syndrome[6, 25].

Androgens

There are anecdotal reports that systemic androgen therapy in women can help dry eye syndrome but there have not been any clinical trials. A topical testosterone cream/gel is in phase 1 clinical trials[3].

Flaxseed oil

Flaxseed oil contains linoleic acid and has been reported to help dry eye. In a trial, one group of patients with meibomian gland dysfunction were given tablets containing linoleic acid (28.5mg) and gama-linolenic acid 15mg.

One group had only lid hygiene and one group had both tablets and lid hygiene. Most improvement was seen in the group receiving both treatments[26].

Surgical and other treatments

Patients whose condition is aggravated by lid abnormalities may benefit from corrective surgery.

For patients in whom artificial tears are not sufficient, punctal occlusion may be effective for both preserving the patient's own natural tears and prolonging the effect of instilled tears. Plugs are initially used and they can be temporary (collagen – a few days to gauge benefit) or semi-permanent (silicone).

They have the advantage of being reversible if epiphora develops. Permanent occlusion with laser or thermal cautery can be performed but this should always follow a trial with plugs as this is not readily reversible.

Anti-inflammatory drugs

There are two main types of anti-inflammatory products used in the eye, steroids and non-steroidal anti-inflammatory products.

Non-steroidal anti-inflammatory drugs (NSAID)

Endogenous prostaglandins play a significant role in the initiation and maintenance of ocular inflammation. They increase the permeability of the blood ocular barrier, affect intraocular pressure and produce miosis and conjunctival hyperaemia. NSAIDs primarily act as cyclooxygenase inhibitors and reduce the formation of endogenous prostaglandins from arachidonic acid, thereby preventing the formation of prostaglandins. There are many valid clinical uses for NSAIDs in ophthalmology but as the commercial products have very few licensed indications, they may be used outside their licensed indications in clinical practice[27] (table 3).

Although these drugs do inhibit intra-operative miosis if instilled pre-operatively they have no intrinsic mydriatic properties and do not replace the use of mydriatic agents for cataract

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