

CURRENT CONCEPTS IN THE THERAPEUTIC APPROACH TO ALLERGIC CONJUNCTIVITIS

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ABSTRACT

Allergic conjunctivitis is an extremely common and often notoriously chronic condition that remains difficult to manage effectively. It is wise to adopt a step-care approach, starting with identifying, avoiding and diluting the antigen, using simple effective therapy like icepacks, and then as the need arises progressing step by step to the top of the therapeutic 'ladder' where the use of steroids and immunosuppressants become unavoidable. Topical antihistamines provide faster and superior relief of symptoms than systemic treatment and have become the treatment of choice in ocular allergic disorders for many practitioners. This overview attempts to simplify the pharmacological treatment options based on the current understanding of drugs and their mechanisms of action. The discussion includes the use of topical antihistamines, vasoconstrictors, mast-cell stabilisers, non-steroidal anti-inflammatory drugs, and corticosteroids.

The drug treatment options for allergic conjunctivitis have markedly expanded over the last few years, providing opportunities for more focused therapy, but unfortunately often leaving both patient and doctor confused over the variety of options. This overview attempts to simplify the pharmacological treatment options based on the current understanding of drugs and their mechanisms of action. Simple therapeutic options will be alluded to in the final suggested 'step-care' approach.

In the topical medical treatment of ocular allergy, it is necessary to deliver a sufficient concentration of the drug to the surface of the eye over a sufficient period to obtain optimal results.

Oral medications, such as antihistamines, on the other hand, control multiple early-phase allergic symptoms in the mucosa of the eyes, nose and pharynx, but unwanted side-effects are common. Topical antihistamines provide faster and superior relief of symptoms compared with systemic treatment and have become the treatment of choice in ocular allergic disorders. However, before reverting to pharmacological intervention, simple (often very effective) measures should be implemented.

NON-PHARMACOLOGICAL INTERVENTION

Identification and avoidance of the allergen

The primary approach to the management of ocular allergic disease should be the education of the patient

and family on the nature of the causative allergens and their environmental control. This is an extensive topic on its own and will not be covered in this review.

Dilution of the antigen

This can be very effective especially in the acute attack or when the ocular surface has recently been exposed to a large dose of allergen. The patient is simply taught to rinse the eyes with a solution of one teaspoon of table salt and half a teaspoon of bicarbonate of soda in a litre of lukewarm, previously boiled, water. Alternatively, instilling synthetic commercial tear drops will dilute the antigen load.

'Cryotherapy'

Simple application of ice in the form of ordinary freezer ice cubes or the commercially available ocular icepacks on the closed eyelids will help in acute cases to reduce conjunctival chemosis and eyelid swelling, aid vasoconstriction and relieve itching.

PHARMACOLOGICAL INTERVENTION

Ophthalmic antihistamines¹

Topical H₁ antihistamines are the most commonly used drugs for the treatment of acute allergic, vernal and atopic conjunctivitis. They are associated with an extraordinarily low incidence of systemic side-effects. Local side-effects are usually related to the preservative benzalkonium chloride, which is found in many of the preparations.

Studies have shown that stimulation of H₁ receptors elicits ocular itching² whereas stimulation of H₂ receptors produces vasodilatation of conjunctival vessels without itching.³ In the eye, H₁ antihistamines effectively reduce histamine-induced itching.

Topical ophthalmic preparations of H₁ antihistamines currently include an alkylamine (*pheniramine maleate*), two ethylenediamines (*antazoline phosphate* and *pyrilamine maleate*), two piperadines (*levocabastine HCl* and *ketotifen fumarate*), a dibenzoxepin (*olopatadine HCl*) and a benzimidazole (*emedastine fumarate*). Pheniramine maleate, antazoline phosphate and pyrilamine maleate are only available in combination with vasoconstrictors, while levocabastine, ketotifen, olopatadine and emedastine are available without a vasoconstrictor.

Pheniramine 0.3%, *antazoline* 0.5% and *pyrilamine* 0.1% have been used since the 1940s.

Levocabastine 0.05% is a long-acting, highly potent, and selective H₁-receptor antagonist. It is 15 000 times more potent than chlorpheniramine in the rat model.⁴ It is clinically effective in reducing itching, hyperaemia and chemosis, and is used up to four times daily.

Olopatadine 0.1% is the first dual-action allergy therapy to receive approval as both an antihistamine and a mast-cell stabiliser. It has been shown to be 1 059 times more selective for H₁ receptors than for H₂ receptors.⁵ Its dosing regimen is one drop twice a day.

Olopatadine prevents histamine-induced inflammatory cytokine production by human conjunctival epithelial cells.

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Emedastine 0.05% is a potent, selective H₁ antagonist. Its selectivity accounts for its low side-effect profile. It can be used up to four times daily to relieve the signs and symptoms of allergic conjunctivitis.

Ketotifen 0.05% is a non-competitive H₁-receptor antagonist. It has also been shown to inhibit the release of leukotrienes, inhibit eosinophil chemotaxis, and suppress eosinophil activation by cytokines.

Table I lists the topical ocular antihistamines available.

Trade name	Manufacturer	Composition	Concentration
Livostin	Janssen-Cilag	Levocabastine HCl	0.05%
Albalon-A	Allergan	Antazoline	0.5%
		Naphazoline	0.05%
Spersallerg	Restan	Tetryzoline	0.04%
		Naphazoline	0.05%
Patanol	Alcon	Olopatadine	0.1%
Emadine	Alcon	Emedastine	0.05%
Zaditen	Restan	Ketotifen fumarate	0.025%

Generic name	Trade name	Manufacturer	Concentration
Naphazoline	Antistin-Privin	Restan	0.5%
Phenylephrine	Prefrin	Allergan	0.012%
Oxymetazoline	Oxylin	Allergan	0.025%
Tetrahydrozoline	Gemini	Restan	0.05%

Although oral antihistamines are widely distributed throughout the body, attaining adequate concentrations in ocular tissue would require inappropriately high oral doses. Because of the additional drying effect on the mucosa, oral antihistamines are rarely used in the treatment of ocular allergic disease.

Side-effects of topical antihistamines

Because of their anticholinergic effects, some topical antihistamines are contraindicated in patients with narrow-angle glaucoma. The mydriatic effect of the vasoconstrictor in combination products could enhance an attack of angle-closure. These combinations may also be responsible for the loss of accommodation and difficulty with near work experienced by some. These combinations should clearly be used with caution in cases with hypertension, cardiovascular disease and poorly controlled diabetes.

Ophthalmic vasoconstrictors⁶

More than a million bottles of vasoconstrictors are sold in the USA every month. Patients regard conjunctival hyperaemia as a significant sign warranting treatment. These medications are successful in reducing conjunctival oedema and hyperaemia. These chemicals can be used alone or in combination with other agents such as antihistamines.

The release of vasoactive amines is responsible for the hyperaemia, tearing, and itching that occur with allergic conjunctivitis. Vasodilation results in endothelial gaping, fluid transudation, chemosis and lid oedema. By constricting the blood vessels, vasoconstrictors are able to alleviate these effects.

Phenylephrine: This is the oldest of the currently available vasoconstrictor agents. It is indicated for use in

ocular allergies in concentrations around 0.12%, whereas higher concentrations are used for mydriasis.

Naphazoline: It is currently available in concentrations ranging between 0.012% and 0.1% and has proven efficacy in reducing conjunctival hyperaemia, discomfort and itching in allergic conjunctivitis. Rebound vasodilation has been associated with vasoconstrictor use. This may result from receptor desensitisation.

Tetrahydrozoline: This is currently available for ophthalmic use in a 0.05% solution. Most eyes whiten within one minute of instillation. The effect of a single application can last for up to 4 hours. Use of this drug has been shown not to alter pupil size or raise intra-ocular pressure (IOP) but rather to lower IOP 30 minutes after use.

Oxymetazoline: Without prescription it is available in a 0.025% solution and has been shown to significantly relieve the signs and symptoms of allergic conjunctivitis.

Table II lists the topical adrenergic modulators available.

Side-effects of topical vasoconstrictors

Indiscriminate non-prescription use of decongestant eye drops can produce acute and chronic forms of conjunctivitis by pharmacological, toxic and allergic mechanisms. To minimise these effects, the solutions should be used as infrequently as possible. Because of the low concentrations, systemic side-effects occur infrequently.

Mast-cell stabilisers⁷

Cromolyn sodium (Opticrom) became the first widely used mast-cell stabiliser for the treatment of allergic conjunctivitis, atopic and vernal keratoconjunctivitis after it was first developed in the 1960s from khellin, an extract derived from the seed of *Ammi visnaga*, an eastern Mediterranean plant used by the ancient Egyptians as an antispasmodic.⁸ Subsequently other mast-cell stabilisers have come on the market like lodoxamide, olopatadine and ketotifen.

Mechanism of action

Mast-cell stabilisers repress type I hypersensitivity reactions by inhibiting the degranulation of mast cells and by preventing the release of histamine and other mediators of hypersensitivity reactions. They have no direct vasoconstrictor, antihistamine or anti-inflammatory actions.

Chromolyn sodium: This compound is beneficial in the treatment of seasonal and perennial allergic conjunctivitis, giant papillary conjunctivitis, vernal and atopic keratoconjunctivitis. It is extremely well tolerated in the eye and the risks of long-term use are negligible. Its long safety record (up to 10 years of continuous use) makes it the drug of choice of many clinicians for long-term use.

Lodoxamide: It has been in use since the mid 1990s and has a similar mode of action to chromolyn sodium. It has been shown to be 2 500 times more powerful than chromolyn sodium in inhibiting the signs and symptoms of allergic eye disease and to powerfully prevent shield ulcers in vernal keratoconjunctivitis. It is a safe drug that can be used four times a day for up to 3 months. Transient burning, stinging, and ocular discomfort were experienced by 15% of patients in clinical trials.

Olopatadine: This formulation contains both antihistaminic and mast-cell stabilising properties, potentially reducing the need for multi-agent therapy. It is administered only twice a day. It is well tolerated and can be used in children 3 years and older.

Ketotifen: Ketotifen is one of the more recently approved anti-allergic eye drops. It has antihistamine, antiplatelet activating factor and mast-cell stabilising features. It may down-regulate mast cell degranulation to below baseline measurements.⁹

Available mast-cell stabilisers are listed in Table III.

Generic name	Trade name	Manufacturer	Concentration
Chromolyn Na	Chromoheal	Hexal	2%
Lodoxamide	Alomide	Alcon	0.1%
Olopatadine	Patonol	Alcon	0.1%
Ketotifen	Ketotifen	Ciba	0.025%

Non-steroidal anti-inflammatory drugs

NSAIDs have shown promise in the management of allergic disorders of the eye. However, only one of them has been approved by the FDA for the relief of itch due to seasonal allergic conjunctivitis, i.e. *ketoralac tromethamine* 0.5% (Acular).

The efficacy of *diclofenac sodium* 0.1% (Voltaren Ophtha) in relieving ocular signs and symptoms of acute seasonal allergic conjunctivitis has been successfully evaluated in several trials. It is available in South Africa, although not registered for this indication.

Flurbiprofen 0.03% (Ocufen) topical ophthalmic solution was found to be superior to vehicle control in reducing hyperaemia and itching following topical antigen challenge.

Corticosteroids¹⁰

Principles of therapeutic use:

- For most allergic disease topical administration is the logical choice, although in the hands of the ophthalmologist supra-tarsal and subconjunctival depo steroids are often valuable in unresponsive cases.

- The minimal effective dose for the shortest amount of time to achieve the desired response is the golden rule. In ocular disease the therapeutic effects of the steroid on the disease, as well as the potential side-effects, i.e. increased IOP and cataract formation must be monitored by an ophthalmologist at a slit lamp.
- The choice of steroid and dosage depends on the severity of the allergic response present. 'Weaker' steroids such as fluorometholone (FML, Flucon) and medrysone are less likely to result in IOP elevations.
- Topical therapy should be tapered slowly over several days to weeks because abrupt discontinuation may lead to a flare up of the allergic condition.

Types of ophthalmic corticosteroids

When the management of topical ocular allergic disease is severe enough to warrant corticosteroid use, it becomes necessary to involve the ophthalmologist to ensure proper monitoring of the treatment and its side-effects.

Prednisolone acetate 1% (*Pred Forte*) is a synthetic analogue of hydrocortisone and is probably the most effective agent in anterior segment inflammation. It is however seldom used in allergic eye conditions.

Dexamethasone 0.1% (*Maxidex, Spersadex*). This drug is 25 times as potent as hydrocortisone and is well suited for severe ocular surface inflammation.

Preparation	Trade name	Concentration
Prednisolone phosphate	Minims Pred Sod Phos	0.5%
Prednisolone acetate	Pred Mild Pred Forte	0.12% 1.0%
Dexamethasone suspension	Maxidex/Spersadex	0.1%
Fluoromethalone suspension	Flucon FML FML Forte	0.1% 0.1% 0.25%
Medrysone suspension	HMS	1.9%

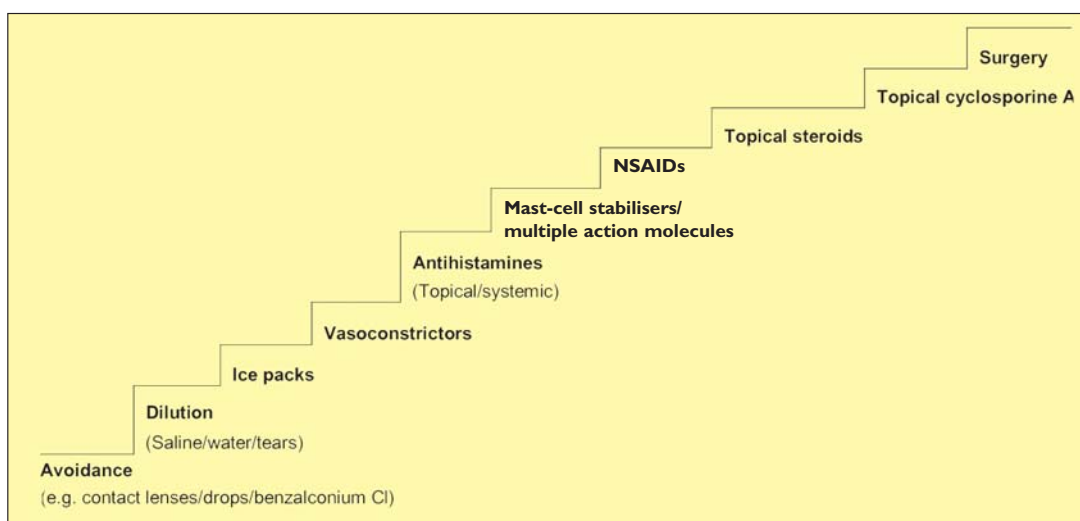


Fig. 1. Step-care management of allergic conjunctivitis.

Fluoromethalone 0.1% (FML, Flucon) is a structured analogue of progesterone and is very effective in reducing ocular surface inflammation with a low potential for IOP elevation. It is therefore a popular choice for surface disease.

Medrysone 1%, another synthetic derivative of progesterone, is the least potent of the available ophthalmic steroids. It is very popular for ocular surface disease as it does not cause a significant rise in IOP.

Loteprednol etabonate 0.2%, available in the USA, represents a 'soft drug' designed to maximise therapeutic effect while minimising side-effects. It has proven to be very effective in the treatment of allergic conjunctivitis. It is however not yet available in South Africa.

Table IV lists ophthalmic corticosteroids.

CONCLUSION

Allergic conjunctivitis is often a chronic condition and remains difficult to manage effectively. It is therefore wise to adopt a step-care approach, starting with identifying and avoiding the antigen and progressing step by step to the top of the ladder where the use of steroids may become unavoidable (Fig.1). Educating the patient to understand the condition and supplying the patient with all the step-care knowledge will aid him or her in controlling symptoms adequately and will therefore reduce dependency on drug therapy.

Declaration of conflict of interest

The author has no conflict of interest.

REFERENCES

1. Abelson MB, Schaefer K, Wun PJ. Antihistamines and antihistamine/vasoconstrictor combinations. In: Abelson MB, ed. *Allergic Diseases of the Eye*. London: WB Saunders, 2000: 202-210.
2. Weston JH, Udell IJ, Abelson MB. H1 receptors in the human ocular surface. *Invest Ophthalmol Vis Sci* 1981; **20**: Suppl, 32.
3. Abelson MB, Udell IJ. H2 receptors in the human ocular surface. *Arch Ophthalmol* 1981; **99**: 302.
4. Abelson MB, Smith LM. Levocabastine: evaluation in the histamine and compound 48/80 models of ocular allergy in humans. *Ophthalmology* 1988; **95**: 1494.
5. Sharif NA, Zu SX, Yanni JM. Olopatidine (AL 4943A): ligand binding and functional studies on a novel, long acting H1-selective histamine antagonist and anti-allergic agent for use in allergic conjunctivitis. *J Ocul Pharmacol Ther* 1996; **12**: 401.
6. Abelson MB, Zbyszynski B. Vasoconstrictors. In: Abelson MB, ed. *Allergic Diseases of the Eye*. London: WB Saunders, 2000: 235-239.
7. Abelson MB, Wun PJ, Nevius JM. Mast cell stabilizers. In: Abelson MB, ed. *Allergic Diseases of the Eye*. London: WB Saunders, 2000: 228-234.
8. Rall TW. Drugs used in the treatment of asthma: the methylxanthine, cromolyn sodium, and other agents. In: Gilman A, Rall T, Nies A, et al., eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 8th ed. New York: Pergamon Press, 1990: 619.
9. Costa JJ, Harris AG, Delano FA, et al. Mast cell degranulation and parenchymal cell injury in the rat mesentery. *Microcirculation* 1999; **6**: 257.
10. Abelson MB, Welch D. Corticosteroids. In: Abelson MB, ed. *Allergic Diseases of the Eye*. London: WB Saunders, 2000: 211-220.

ATTENTION ALLSA MEMBERS

This is to inform you that the 2006 ALLSA Annual General Meeting (AGM) will be held at the Sun City Convention Centre during the ALLSA Congress.

TIME: 17h30

DATE: Friday 8th September 2006

VENUE: Sun City Convention Centre

AGENDA

1. Minutes of the previous meeting

2. Matters arising

3. Secretary's report

4. Treasurer's report

5. Portfolio Reports

Journal

Research

Education/Training

Policy/Advocacy

6. General

7. Announcement of the new Excom

Dr Sharon Kling

Dr Adrian Morris

Professor Heather Zar

Professor Mohamed Jeebhay

Dr Sharon Kling

Dr Andrew Halkas