EBSCR

1. RxFiles OTC (Over the Counter) Products Comparative Chart. March 2012.

Source description

RxFiles is an academic detailing program initiated in 1997 in Saskatoon, Saskatchewan. They provide Drug Comparison Charts, newsletter reviews, Q&As, and trial summaries for physicians, pharmacists and other healthcare providers. The OTC Products drug comparison chart was prepared by Jensen B, Regier L, Downey S, Karlson P, and Taylor J, updated March 2012. Primary reviewer was Dr. Jeff Taylor, University of Saskatchewan, College of Pharmacy & Nutrition. The primary referencing for the chart came from

1) Patient Self-care, first edition. CPhA 2002
2) Compendium of Nonprescription Products. CPhA 2002-3.
3) Therapeutic Choices, fifth edition. CPhA 2007.
4) Drug Information Handbook, 18th edition. APhA 2009.
5) Treatment Guidelines: Drugs for Allergic Disorders. The Medical Letter 2010 pg 9-18
6) Reid RL, et al. SOGC update 2009. JOGC 2009.

Summary

Topical antihistamines are recommended when conjunctivitis is the only symptom, otherwise, oral antihistamines relieve all (to some extent) allergic symptoms except nasal congestion. Specifically for ophthalmic topical applications, prescription preparations are generally more efficacious. Single agent H1 blockers includes Livostin® (levocabastine). H1 blockade and mast cell stabilizer topical preparations include Zaditor® (ketotifen) and Patanol® (olopatadine). The authors recommend instilling 1-2 eye drops QID, and caution that the product expires in 1 month after opening. Topical antihistamines are also sold in combination with topical decongestants, however they are not recommended for use do to the rebound effect.

Comments/critical appraisal

Internal validity for this resource is well established, using a variety of references such as treatment guidelines, evidence-based evaluations, and clinical trials, with a total of 17 articles specifically focusing on antihistamine therapy. There is no bias, since the reviewers are not the authors. External validity is also strong, as this chart can be applied to all populations, including seniors, pediatrics, pregnancy and lactation.

2) Owen C, Shah A, Smeeth L, Sheikh A. Topical treatments for seasonal allergic conjunctivitis: systemic review and meta-analysis of efficacy and effectiveness. Br J Gen Pract. 2004 June 1; 54(503): 451–456.

Study objectives

To assess the effectiveness and relative efficacy of topical treatments for the management of seasonal allergic conjunctivitis.

Scope

Participants: Subjects with allergic conjunctivitis.
Interventions: Trials that compared the use of topical mast cell stabilizers with placebo, topical antihistamines with placebo and topical mast cell stabilizers with topical antihistamines
Outcomes: Efficacy of topical mast cell stabilizers or topical antihistamines compared to placebo or each other
Duration: Variable from 7 days to 4 months.

Methods

Type of trials: Double blinded, randomized controlled trials
Inclusion: concealed allocation of treatment; contained subjective assessment of treatment efficacy; documented patient inclusion criteria
Trial Search: One reviewer completed the search, identified from the Cochran Eyes and Vision Group trials register, Cochrane central register of trials on the Cochrane Library, MEDLINE, and EMBASE
Selection of Studies: Two reviewers extracted data

Main results

Topical mast cell stabilizers versus placebo: Five of eight studies reported an improvement in a variety of subjective symptoms while using topical sodium cromoglycate preparations, remaining three trials found no difference in symptoms between treatment groups. Based on a random-effects estimate those using topical sodium cromoglycate were 17 times more likely to perceive benefit than those using placebo. No important adverse effects were reported with the active treatment, aside from stinging upon instillation in both groups when phenylethanol was used. Three of five studies showed statistically significant improvement when using nedocromil sodium versus placebo. The one trial using lodoxamide tromethamine reported significantly fewer symptoms compared to placebo.

Topical antihistamines versus placebo: Formal meta-analysis was not possible as most studies did not tabulate the mean scores and error associated with these measures. Most studies showed improvement in symptoms post-provocation, especially for symptoms of itchiness compared to placebo. No evidence points to an antihistamine that provided better outcomes.

Topical mast cell stabilizers versus topical antihistamines: Formal meta-analysis was not possible as most studies did not tabulate the mean scores and error associated with these measures. No statistically significant differences were found between the treatment groups.

Conclusions

Trials showed that both topical mast cell stabilizers and topical antihistamines are more effective than placebo, however there was insufficient evidence to support the use of once class of active medication over another.

Comments/critical appraisal (including assessment of internal and external validity)

The validity of this meta-analysis is questionable. The participants studied and exclusion criteria were not described, leaving the reader with limited information. There was no mention about contacting authors about missing information or unpublished data, therefore it is likely that some important trials may have been missed. Since most of the trials used were not well done, a proper meta-anaylsis could not be performed for two of the three comparisons. Although the authors drew conclusions about the agents' efficacy compared to placebo, the more important question was about the efficacy of the two agents compared to each other, which the authors could not answer. Larger studies would need to be performed to assess the two active ingredients to determine which one may be better than the other.

3) Patient Self-Care Helping Your Patients Make Therapeutic Choices, second edition. Canadian Pharmacists Association 2010.

Source description

The Patient Self Care textbook is composed by several authors, a practitioner review board, and editorial board, and published by the Canadian Pharmacists Association. Season allergic conjunctivitis is found in chapter 15, Conjunctivitis, by Anne M Friesen (BScPharm, MSc). The description and limitations of information has been states as such:

"Although based on the best available evidence, Patient Self-Care also contains selected information representing the opinions and experience of individual authors. … Users should be aware that the text may contain information, statements and dosages for drugs different from those approved by the Therapeutic Products Directorate, Health Canada. The manufacturers' approval has not been requested for such information. … Healthcare professionals are encouraged to seek additional and confirmatory information to meet their practice requirements and standards as well as the information needs of the patient."

Summary

Topical antihistamines are recommended as second-line treatment of mild to moderate seasonal allergic conjunctivitis. The antihistamine, pheniramine, comes in combinations with the following decongestants: naphazoline, phenylephrine, oxymetazoline, and tetrahydrozoline. Due to the decongestants, these products should not be used for greater than 10 days, at which point rebound redness could occur. The expected clinical benefit of the topical antihistamine includes decrease in eye redness, itching, eyelid edema and tearing. The drops are instilled as 1-2 drops q3-4h prn, up to four times daily.

Comments/critical appraisal

As stated in the source description, some information provided in this resource comes from the opinions and experience of individual authors. These authors, however, are experts in their field and base the information on the best available evidence. The CPhA states they, "[employ] a rigorous review process to ensure that the information is accurate and unbiased". The content is extensively reviewed by pharmacist editors and reviewers who are experts in the particular clinical field. CPhA also "asks authors and reviewers to disclose any potential conflicts of interest, [and do] not accept funding from pharmaceutical manufacturers for any content developed". The internal validity is therefore unbiased and composed by an expert in the field. The information can be applied to the general population, with the caution that healthcare professionals should seek additional information when making a clinical decision with a patient.

4) Mortemousque B, Jacquet A, Richard C, et al. Randomised double masked trial comparing the efficacy and tolerance of 0.05% mequitazine eye drops versus 0.05% levocabastine and placebo in allergic conjunctivitis induced by a conjunctival provocation test with Dermatophagoides pteronyssinus. *Br J Ophthalmol* 2004; 88:336-40.

Study objectives

The main objective was the effect of the drugs after the conjunctivitis provocative test (CPT) at visit 2 (curative effect). The second objective was assessing the response to CPT after repeated instillations of the treatment.

Methods

o Design: Double masked, randomized, single centre non-inferiority study

o Allocation: Three parallel treatment groups of healthy volunteers, 20 subjects in each group

o Blinding: Double blinded. The three treatment drops were packed in identical 3mL bottles, delivering 30uL drops.

o Follow-up period: Three weeks, no patients were lost to follow-up.

o Setting: single center study in France

o Participants: Sixty participants above 18 years of age of both gender. Patients had an at least two year history of allergic conjunctivitis to house dust mites, confirmed by a positive prick test to *Dermatophagoides pteronyssinus* and/or specific IgE $\geq$ grade 3 (RAST) within the previous six months, and by a positive screening conjunctival provocation tests (CPT) to dust mites (<100RI/mL). At inclusion, patients were symptom free and had a normal ocular examination with corrected far visual acuity >0.6 and intraocular pressure <21mmHg.

o Intervention: Twenty subjects received mequitazine 0.05%, 20 subjects received levocabastine 0.05%, and 20 subjects used placebo. Subjects were not allowed contact lenses or any other medication other than the trial medication during the study. At visit 2, conjunctivitis was induced (using CPT), immediately followed by instillation of a single drop of the study treatment. Scoring was assessed 10, 15, and 60 minutes post CPT. Subjects then instilled one drop twice daily of the study treatment for 2 weeks. After 2 weeks of this preventative therapy, CPT was done with increasing doses of allergen until a positive reaction was elicited.

o Outcomes: Primary outcome was the sum of the scores for redness and itching 10 minutes after the instillation of the medication. Secondary outcomes included the reaction symptom scores at visit 2 and visit 3.

o Patient follow-up: CPT screening was done at baseline, at visit 2 (V2) 1 week later, and at visit 3 (V3) 2 weeks after V2.

o Funding: All three eye drops were provided by Chauvin Bausch & Lomb

Main results

The primary outcome looked at redness and itchiness. The mean score for these two parameters 10 minutes after treatment instillation was 2.6 for placebo, 2.3 for levocabastine and 2.4 for mequitazine group, with no statistically significant difference between the three groups. During visit 3, there was no statistically significant difference between treatment groups for redness, itching, or redness + itching scores before CPT. Once CPT was started on visit 3, sixteen of the 20 mequitazine patients had a negative CPT at the initial threshold antigen concentration, 11 in the levocabastine group and 8 in placebo ($p=0.035$). In nine patients on mequitazine, the threshold concentration was two or more levels above the baseline, compared to 4 in levocabastine and 3 in placebo. Mequitazine was significantly better than placebo ($p=0.01$) but not than levocabastine ($p=0.10$).

Conclusions

The study showed that mequitazine was not better than levocabastine and placebo for curative purposes, but it was significantly better for prevention.

Comments/critical appraisal

This was a very small study sample, which could have affected the results. Standardization of the allergen was well done, using the conjunctival provocation test (CPT). This allows reproducible quantitative measurements of the allergic response using a well defined grading system. However, the study states that the doses given during CPT may have been too low, resulting in a mild reaction compared to a natural environmental reaction. The definition of threshold doses needs to be better defined, as well as the timing of drug instillation and effect measurement. After the testing was complete, the allergen was rinsed from the eye, which could have resulted in a higher placebo effect. Only redness and itching were measured, and the study did not look at tearing or discharge. This study should be used as a guide for future trials, however there need for improvement in study design. Overall, this study has many flaws and is not very valid.

5) Mah F, Rosenwasser L, Townsend W. Efficacy and comfort of olopatadine 0.2% versus epinastine 0.05% ophthalmic solution for treating itching and redness induced by conjunctival allergen challenge. Curr Med Res Opin 2007; 23(6): 1445-52.

Study objectives

To compare the efficacy and comfort of olopatadine 0.2% with epinastine 0.05%, in the prevention of ocular itching associated with allergic conjunctivitis following conjunctival allergen challenge (CAC).

Methods

- o Design: Double-masked, randomized, placebo-controlled study
- o Allocation: 92 subjects divided into four groups to receive one drop of study medication into each eye: olopatadine 0.2%/placebo (n=27), epinastine 0.05%/placebo (n=28), olopatadine 0.2%/epinastine 0.05% (n=28), placebo/placebo (n=9).
- o Blinding: Double blinding
- o Follow-up period: Seven weeks
- o Setting: Single center, clinical setting of Ophthalmic Research Associates, North Andover, MA
- o Participants: Average age of 41 years, equal male and female
- o Intervention: Visit 1 screened subjects for positive ocular allergic responses. Visit 2 confirmed these responses. At Visit 3, subjects were randomized into one of 4 treatment groups. At Visit 4, subjects were challenged 5 minutes after drop instillation to evaluate onset of action. Subjects were not allowed to use any topical ocular medication (other than study medication) for the duration of the study.
- o Outcomes: Results of onset of action challenge in visit 4 (ocular itching and redness) and drop comfort
- o Patient follow-up: 92 enrolled, 91 subjects completed the study. One participant failed to report to visit 3. An intention-to-treat protocol was followed.

Main results

Efficacy of Itching: Both active treatments were statistically superior to placebo at preventing ocular itching at all assessment time points ($p < 0.001$ for both treatments). There was no significant difference in mean itching scores at 3 min post-challenge. Olopatadine 0.2% exhibited significantly lower ocular itching scores compared to epinastine 0.05% at 5 min ($p = 0.024$) and 7 min ($p = 0.003$) post-challenge.

Efficacy of Redness: Olopatadine 0.2% demonstrated statistically significant lower redness for all three time points, compared to epinastine 0.05% only demonstrating statistically lower redness scores at seven minutes ($p < 0.002$).

Comfort: Olopatadine 0.2% showed significantly more comfort ($p<0.05$) at 2 and 5minutes post dose compared to placebo. There was no difference between epinastine 0.05% and placebo. Comfort scores for olopatadine 0.2% were statistically better at the 1minute mark ($p=0.03$) compared to epinastine 0.05%, but no difference at 2 and 5minutes.

Conclusions

Olopatadine 0.2% and epinastine 0.05% are both effective topical agents for seasonal allergic conjunctivitis. Olopatadine 0.2% was found to be superior to epinastine 0.05% at preventing itching and redness, and was also a more comfortable treatment.

Comments/critical appraisal (including assessment of internal and external validity)

The results of this trial were valid, with the patients being randomized, equal at the start of trial and treated equally during the study. The investigators were blinded and followed intention-to-treat protocol, accounting for all patients who started the trial. Although there were only 92 subjects, a fairly small trial, results were significant. The trial was well designed, the results valid, therefore I would trust the outcomes.

Place in Therapy

Topical ophthalmic antihistamines function as selective histamine receptor antagonists used to decrease symptoms of itching and redness during seasonal allergic conjunctivitis. Based on three tertiary sources and 2 primary sources, topical antihistamine therapy fall third line in place of therapy. All over-the-counter products in Canada are available in combination with decongestants, which have also been placed later in line of use. These products do not work at the source of mast cell degranulation, thus they only work to relieve symptoms rather than the underlying cause of the allergen. Due to the topical formulation, there is little systemic absorption, and low systemic adverse effects. Overall, topical antihistamines have minimal efficacy and good safety.

Therapeutic Option	**Mechanism of Action**	**Onset of Effect/Duration of Treatment**	**Adverse Effects**	**Contraindications**	**Drug or other Interactions**	**Risk Level for Drug Interactions**	**Convenience / Cost**
Topical Antihistamines	Upon exposure to an allergen, an IgE mediated response causes mast cell degranulation, which in turn causes immediate release of histamine. Histamine is the primary mediator of itching, redness, and swelling. Topical ocular antihistamines are selective histamine (H1) receptor antagonists responsible for decreasing symptoms.	Onset of Action: 10-15 minutes Duration of Action: 8 hours	-mild transient burning or stinging -pruritis -hyperemia -foreign body sensation -superficial keratitis -lid edema -dry eye -lid dryness -lid spasm -photophobia -asthenia -headache -taste perversion -fatigue -insomnia	**Pregnancy:** Risk factor C **Lactation:** Excretion into breastmilk unknown, use with caution **Renal:** n/a **Hepatic:** n/a **Other:** Hypersensitivity to the active ingredient or any component of the formulation	Data suggests there are no drug interactions, mostly due to low systemic exposure.	Low risk	Recommended dose is one to two drops in each affected eye BID. Cost: moderate $18.99/15mL