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Topical antihistamines in the treatment of seasonal allergic rhinoconjunctivitis with equal or greater effectiveness when compared to systemic antihistamines in monotherapy

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Abstract

Background: It has been estimated that seasonal allergies affect up to approximately 44% of the population. Many people compromise the quality of their lives in order to function on a day to day basis. There are several treatments that are available in alleviating symptoms related to seasonal allergies, but many people have difficulty adhering to certain recommended regimens. Intranasal corticosteroids have been thought of as the first line of therapy in the treatment of seasonal allergies, but these require daily treatments. Systemic antihistamines, on the other hand, provide allergic relief on an as-needed basis, but are subject to a higher possibility of side effects as they are systemically metabolized. Topical antihistamines are a class of medications that could possibly provide similar, if not better, effectiveness in symptomatic control of seasonal allergies.

Methods: The focus of this study was to review clinical trials providing comparison between topical antihistamines and systemic antihistamines. Clinical trials within the last fifteen years comparing topical antihistamines with systemic antihistamines and with placebos, were carefully selected and analyzed. Double-blinded and randomized clinical trials of specific topical antihistamines and systemic antihistamines were identified by a systematic literature search using MEDLINE, CINAHL, and PUBMED search engines.

Results: Based on the seven randomized, double-blinded, and placebo controlled clinical trials, the efficacy of topical antihistamines was significantly greater than systemic antihistamines. Both topical and systemic antihistamines significantly improved symptoms compared to placebo.

Conclusion: Overall, topical and systemic antihistamines reduced seasonal allergy symptoms, particularly allergic rhinoconjunctivitis. This review confirms the effectiveness of topical antihistamines when compared to systemic antihistamines.

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Faculty Advisor: Latha Reddy MS, PA-C

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Biography

Young Cho is a native of Seattle, WA where he attended the University of Washington and completed his Bachelors of Nursing at Seattle Pacific University. After completion of his undergraduate degree, he worked as a registered nurse in the medical telemetry and renal units at Providence Everett Medical Center for three years. He then worked for another year at The Everett Clinic in the Otolaryngology department. Wanting to advance his career, he is pursuing a Masters in Physician Assistant Studies and is expected to graduate in the summer of 2009.

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Abstract

Background: It has been estimated that seasonal allergies affect up to approximately 44% of the population. Many people compromise the quality of their lives in order to function on a day to day basis. There are several treatments that are available in alleviating symptoms related to seasonal allergies, but many people have difficulty adhering to certain recommended regimens. Intranasal corticosteroids have been thought of as the first line of therapy in the treatment of seasonal allergies, but these require daily treatments. Systemic antihistamines, on the other hand, provide allergic relief on an as-needed basis, but are subject to a higher possibility of side effects as they are systemically metabolized. Topical antihistamines are a class of medications that could possibly provide similar, if not better, effectiveness in symptomatic control of seasonal allergies.

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Keywords: seasonal allergic rhinitis, allergic conjunctivitis, azelastine, olopatadine, cetirizine, loratadine, desloratadine

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INTRODUCTION

Seasonal allergies impact the lives of many people and can severely affect the quality of life in day to day activities. It is estimated that allergies affect up to 44% of the United States population.¹ In 1997, estimates showed that direct costs related to allergies totaled approximately \$4.5 billion/year along with 3.8 million missed work and school days.¹ Many people generally side with the belief that a systemic medication works best in controlling allergic symptoms while not being fully apprised of the fact that other treatment modalities are available to them that do not require systemic absorption for effectiveness.

Generally speaking, allergies can be categorized into perennial and seasonal allergies. Causes of perennial allergies may include dust mites, cat and dog dander, and mold. Seasonal allergies usually occur during specific times of the year in response to certain allergens that are present in the environment. For example, in the northwest United States, grass pollen is widely prevalent during the months of May to July. Populations sensitive to grass allergens may develop symptoms during these months. Perennial allergies are thought to be more difficult to treat compared to seasonal allergies which can be managed medically in anticipation of the seasonal months.

Allergies are known to be a humoral mediated response of the immune system triggered by an allergen. When an allergen, such as pollen from grass or ragweed, triggers a hyperresponsive reaction in a hypersensitive person, a cascade of events unfolds.

The allergen initially forms peptides which cause cytokines to be formed. IgE, the allergy driven class of immunoglobulin antibodies, is formed in response to these cytokines by B cells. These antibodies bind to mast cells and basophils causing a release of granules within the cell. The granules contain histamine and leukotrienes among many other allergic and inflammatory mediators. Histamine binds to certain receptors that have been identified throughout the body. These inflammatory mediators, in turn, cause a series of allergic reactions. Common allergic reactions can involve edema of the tissues (such as in the face), oral mucosa, sneezing, rhinorrhea, redness, tearing and swelling of the conjunctiva, dermatitis, and sometimes even bronchoconstriction of the airway.

Seasonal allergies have historically been treated with first-generation systemic antihistamines like diphenhydramine (Benadryl). These were effective, but also had a side effect profile of causing sedation and drowsiness. Many people had difficulty functioning in their daily routines because of these sedative effects. Second-generation oral antihistamines, such as loratadine (Claritin) and cetirizine (Zyrtec) were then developed with a less sedating side effect profile. Other methods of medical management involve intranasal corticosteroids such as fluticasone (Flonase). Nasal corticosteroids involve a daily regimen and take about a week to take effect with optimal drug levels peaking at two weeks. Corticosteroids provide a localized anti-inflammatory effect in the nasal and sinus pathways. Antihistamine nasal sprays and eye drops work within minutes and are localized to the site of action. These topical antihistamines do not require daily usage and they provide the benefits of controlling allergic symptoms localized to the nasal and sinus passages and they also help control ocular symptoms without having to be systemically absorbed. Table 1 lists common topical and oral antihistamines available either over-the-counter or by prescription.

Many patients have difficulty adhering to the daily regimen of using an intranasal corticosteroid. Other patients avoid using oral antihistamines to control allergy symptoms in order to avoid systemic absorption and the risk of side effects such as somnolence and fatigue. Although topical antihistamines have been proven to provide symptomatic relief of allergies, many patients are under the presumption that seasonal allergies are best treated in the form of a pill without recognizing the potential adverse systemic effects of the medication. Because some patients cannot tolerate steroids, whether it is due to epistaxis, adherence, or intolerability, it seems reasonable to prescribe topical antihistamines over systemic antihistamines to provide immediate effective relief from seasonal allergic rhinoconjunctivitis. The aim of this review is to evaluate the effectiveness of topical antihistamines compared to systemic antihistamines in monotherapeutic symptomatic treatment rhinoconjunctivitis.

METHOD

An exhaustive literature search was executed using MEDLINE, PUBMED, and CINAL to identify studies treating patients with seasonal allergies and comparing the use of topical antihistamines to systemic antihistamines.

As it is difficult to locate several randomized placebo-controlled trials comparing topical antihistamines to systemic antihistamines, multiple different methods were used in the search. This review is part of a series that included antihistamine medications and seasonal allergic rhinitis and conjunctivitis search terms. Selected studies also had to meet the criteria of involving the treatment of patients suffering from seasonal allergic rhinoconjunctivitis independent of perennial allergies. Broad definitions of allergies and treatments were used to include a large pool of studies. From there, specific terms such as intranasal antihistamines, ocular antihistamines, and oral antihistamines were used to narrow the search without much

success. To further focus the review, a specific topical antihistamine, such as azelastine and a systemic antihistamine such as cetirizine, were used in the search. Each topical medication was paired with a different systemic medication until most pairings were exhausted. Certain trials were also included if they investigated the efficacy of a topical version of the same oral drug in the treatment of seasonal allergies.

Studies that were excluded involved patients on other medications which could alter the results of the effects of antihistamines. Several studies were excluded based on the fact that corticosteroids were given in conjunction with antihistamines as part of the study design. Also excluded were reviews that included research of co-morbid conditions in patients with allergies, such as autoimmune conditions, pulmonary conditions, and cardiac illnesses, among others. Single histamine trials were also not pertinent to this review. Additionally, adjunctive studies that combined topical and systemic antihistamines compared to systemic antihistamines alone were ruled out. Fortunately, the studies yielded by the search were all randomized controlled trials.

RESULTS

Effective outcomes were measured using a scoring system based on nasal or ocular allergy symptoms. The intranasal trials used a scoring system based on the design of the study. For example, the Total Nasal Symptom Score (TNSS), which consisted of runny nose, sneezing, nasal itching, and nasal congestion to measure the effectiveness of the medications in treating allergic rhinitis, was used by three of the published studies for this review. The TNSS was based on a scoring system of 0-3 with “0” representing no symptoms and “3” representing severe symptoms. Since the TNSS was generally consistent in the intranasal studies, overall outcomes were combined. The ocular trials were based on a scoring assessment of conjunctival redness

and itching. Although the two studies measured the same reaction and were useful in determining the results of this review, the scoring methods differed and each study outcome had to be analyzed individually.

The majority of the studies were of good quality with a sizeable number of subjects. A single study in this trial used only 26 patients as part of its subject group. That same study was vague in reporting on its methods and details. The other studies clearly reported the flow of the participants through the trials, reported a large enough sample size, and utilized randomization methods. Most of the trials occurred within a relatively short time frame with the longest being 35 days and the shortest being two weeks. Two of the intranasal studies were designed in a similar fashion with the objective of the most recent one, referred to as ACT II (Azelastine Cetirizine Trial), conducted to confirm the results of the first study referred to as ACT I.

Seven potentially relevant studies were screened and identified. Of these, six were included in the systematic review. Table 2 summarizes the included studies and provides information on patients, interventions, and outcomes.

With the exception of the Korsgren et al study, details of the intervention and comparison groups were available from the papers. The interventions were similar in the studies in that they were effective in treating allergy driven symptoms. Korsgren et al was unique with regards to the fact that they used an intranasal formulation of cetirizine, which is normally taken orally, to compare the effects of the medication. Table 3 lists a comparative evaluation of overall nasal symptom scoring per study methods.

Korsgren et al studied the effects of oral cetirizine compared to an intranasal formulation of cetirizine in treating allergic rhinitis. This study randomized 36 patients into two treatment groups over three 12-day treatment periods separated by two-week washout periods.² Thirty-five

subjects received oral cetirizine, 34 received intranasal cetirizine, and 35 received placebo.² Using a Total Nasal Symptom Scoring Scale (TNSS), scores were recorded during each treatment period. This study directly exposed the patient to a seasonal allergen during each treatment period.² The trial reported the topical cetirizine group to have a mean TNSS of 1.50 in the morning, 3.76 ten minutes after the allergen challenge, and 1.51 in the evening.² The oral cetirizine group showed a mean TNSS of 1.14 in the morning, 3.25 ten minutes after the allergen challenge, and 1.14 in the evening. The placebo group reported a mean TNSS of 1.26 in the morning, 5.15 ten minutes after the allergen challenge, and 1.19 in the evening.²

In 1995, Charpin et al investigated the effects of azelastine nasal spray compared to oral cetirizine. This trial randomized 129 patients into two treatment groups. Using a Total Symptom Score of the Investigator (TSSI), they found negligible improvements in the cetirizine group (n=56) over the azelastine group (n=54). From baseline assessments, the azelastine group showed a 47% decrease in TSSI and there was a 55% decrease in the cetirizine group. Additionally, at day 14 the TSSI showed a 61% decrease for azelastine groups and 67% decrease for cetirizine groups.³ When patients rated their symptoms according to a daily self-assessment scoring sheet provided by the study and labeled as the Visual Analogue Scale (VAS), the VAS recordings of individual symptoms showed that azelastine was significantly better than cetirizine for the relief of nasal stuffiness (azelastine -13.97 ± 1.15 ; cetirizine -9.38 ± 0.94) and rhinorrhea (azelastine -14.71 ± 0.79 ; cetirizine -11.74 ± 0.94).³

The Berger et al (ACT II) and Corren et al (ACT I) papers provided near similar methods, interventions, and outcomes despite utilizing different treatment population groups. Corren et al randomized 307 patients to either receive azelastine (n=152) and a placebo pill or placebo nasal spray and cetirizine (n=155).⁴ They compared using azelastine intranasal spray to

that of cetirizine oral medication in the treatment of seasonal allergic rhinitis. Patients were studied over a two-week treatment period in both studies. Using the Total Nasal Symptom Score (TNSS), Corren et al found that, the TNSS demonstrated overall improvement via a decrease in the score throughout the two week study. There was a 29.3% improvement with azelastine nasal spray compared to one of 23.0% with cetirizine relative to baseline assessments.⁴ The onset of action was similar at 15 minutes for both azelastine and cetirizine, but at 60 minutes and 240 minutes, improvements in TNSS favored the azelastine group.⁴

The Berger et al (ACT II) study randomized a total of 354 patients to be included in the trial. Like the ACT I study, one group was randomized to receive azelastine nasal spray (n=179) and a placebo pill and the other group received cetirizine (n=175) and a placebo nasal spray.⁵ There was a 24.2% improvement with azelastine nasal spray and a 19.2% improvement with cetirizine from baseline symptom assessments, with both groups experiencing increased improvements of TNSS throughout the duration of the trial.⁵

Horak et al performed a 2006 study in Vienna, Austria comparing the effects of azelastine nasal spray and desloratadine tablets. Forty-five patients completed the randomized double-blinded placebo controlled study. The participants were randomized into three groups with azelastine nasal spray (n=15) and a placebo tablet in one group, desloratadine (n=16) and a placebo nasal spray in another, and a placebo nasal spray and placebo tablet (n=15) in the final group.⁶ Horak et al used a Major Nasal Symptom Score (MNSS) to evaluate the effectiveness of the medications. MNSS incorporates the total scores of sneezing, rhinorrhea, and nasal itching.⁶ Results of the study show that azelastine was superior to desloratadine in decreasing MNSS and TNSS. Azelastine showed a -2.1 ± 2.1 change and desloratadine showed a -1.2 ± 2.1 change from baseline MNSS symptoms in treating seasonal allergic rhinitis.⁶

Abelson and Welch evaluated the effectiveness of olopatadine ophthalmic solution to that of loratadine in the treatment of allergic conjunctivitis. Their trial consisted of 29 patients which were randomized into two treatment groups. Groups were to receive one loratadine tablet and one drop of olopatadine in one eye and one drop of placebo in the contralateral eye (n=15) or placebo tablet and one drop of olopatadine in one eye and placebo in the contralateral eye (n=14).⁷ Subjective itching values were used to measure the effectiveness of the antihistamine medications at 3, 7, and 10 minutes in the treatment of allergic conjunctivitis. Significant differences were seen in favor of olopatadine compared to loratadine. At 3 minutes, itching values for loratadine were 0.8 compared to 0.5 for olopatadine. At 5 minutes, itching values for loratadine were 1.2 compared to 0.5 for olopatadine and at 10 minutes the value for loratadine was 0.8 and 0.4 for olopatadine.⁷

Crampton evaluated a similar trial comparing ketotifen ophthalmic to desloratadine in treating allergic rhinoconjunctivitis. Eighty two patients were randomized into three separate groups. Groups received either ketotifen and a placebo tablet (n=27), desloratadine and a placebo eye drop (n=27), or desloratadine and ketotifen (n=26).⁸ Crampton used a redness and itching scoring system on a scale from 0 to 4 (0 = none to 4 = severe) and a nasal symptom scoring system (sneezing, rhinorrhea, post nasal drip, nasal congestion, palatal pruritus) to assess seasonal allergic rhinoconjunctivitis. The study found that ketotifen and ketotifen/desloratadine groups had significantly lower ocular itching scores than the loratadine group alone while ketotifen alone showed significantly less total ocular redness compared to the other groups.⁸ At 10 to 40 minutes, nasal symptom scores were greater in the ketotifen/desloratadine group compared to that of ketotifen or desloratadine alone, but at 50 minutes, the group that received ketotifen/desloratadine had better results than ketotifen alone.⁸

DISCUSSION

The primary goal of this review was to examine the effectiveness of topical antihistamines in comparison to the effectiveness of systemic antihistamines with regards to the treatment of seasonal allergy symptoms. This systematic review provides support for the use of topical antihistamines over systemic antihistamines in treating seasonal allergic rhinoconjunctivitis.

Comparisons between antihistamines remains a difficult area to search due to the dearth of completed studies comparing the delivery systems for antihistamines. Significant attempts were made to identify studies in any language. Currently, the standard therapy for seasonal allergies begins with intranasal corticosteroids and then usually follows with oral antihistamines. Many people have difficulty adhering to the daily regimen of using intranasal steroids for the desired effect of treating seasonal allergies. Secondly, oral antihistamines have proven to be beneficial but require systemic absorption and can render a patient more prone to unwanted side effects. With the exception of Charpin et al, the reviewed studies have shown topical antihistamines providing a greater effect on symptoms than oral antihistamines.

Patients in all the studies were healthy without any co-morbid conditions. Ages of the subjects ranged anywhere from 12 to 74 years old. All were required to have a history of seasonal allergies and either underwent allergen skin testing or had a documented positive allergy skin test.

Corren et al conducted their study in the fall of 2004. Berger et al conducted their multicenter trial during the 2005 spring season. Charpin et al did not specify whether the patients were directly exposed with allergens to elicit an allergic response or whether their study was conducted during a specific season of the year. Horak et al used the Vienna Challenge

Chamber (VCC) to expose the trial population to a controlled grass pollen concentration. VCC is a validated environmental exposure unit that allows allergen challenges in a controlled environment.⁶ Abelson et al and Crampton used a conjunctival allergen challenge model in which the eyes were directly exposed to seasonal allergens to elicit an allergic response.

Korsgren et al conducted their study during the pollen-free Scandinavian winter months and directly treated their patients with controlled allergen challenges.² Also, determining which groups received placebo was difficult to identify from the study. The assumption was made that during each treatment period, the patients would switch to receiving a different modality of the drug. For example, if the subject had received oral cetirizine and an intranasal placebo in the first treatment group, they would then receive either a placebo tablet and cetirizine intranasal spray or placebo tablet and placebo intranasal spray for the successive treatment periods.

In the ACT I and ACT II studies, the most common side effect reported for azelastine was a bitter taste.^{4,5} The most common reported side effect for cetirizine was somnolence.³⁻⁶ No serious adverse reactions were reported in any of the studies.

There is no accepted ideal scoring system in assessing the outcomes of allergies. The Total Nasal Symptom Scoring (TNSS) system appears to be the most commonly used outcome method in quantifying an allergic rhinitis response among patients. The ocular studies used their own assessment scales in determining symptoms for allergic conjunctivitis. Abelson et al placed more emphasis on itching when assessing for ocular symptoms while Crampton used an equally weighted itching and redness scale.

CONCLUSION

These studies used specific antihistamine medications to compare treatment options for seasonal allergic rhinoconjunctivitis. Since all the topical and oral antihistamines that are available were not tested, we can only generalize the effectiveness of the other untested medications since the main mechanism of action is similar for these classes of drugs.

Presently, patients are prescribed intranasal corticosteroids as the initial treatment of choice with oral antihistamines to be used on an as-needed basis. While long term results may be similar in effectiveness, most patients prefer immediate relief from their symptoms as well as decreased likelihood of systemic side effects. Based on this literature review, topical antihistamines are a reasonable treatment of choice for seasonal allergic rhinoconjunctivitis. Future studies would be worthwhile to compare other modalities of treatment for seasonal allergies. The development of a standardized scoring system to evaluate allergic symptoms would also be beneficial for future research studies.

Table 1 | Common Antihistamines

Oral Antihistamines Brand name (generic)	Intranasal Antihistamines Brand name (generic)	Ocular Antihistamines Brand name (generic)
Claritin (loratadine) Clarinex (desloratadine) Allegra (fexofenadine) Zyrtec (cetirizine) Xyzal (levocetirizine) Benadryl (diphenhydramine)*	Astelin (azelastine hydrochloride) Astepro (azelastine hydrochloride) Patanase (olopatadine)	Zaditor (ketotifen) Optivar (azelastine hydrochloride) Patanol (olopatadine) Pataday (olopatadine) Elestat (epinastine)

*1st generation antihistamine

Table 2 | Study Characteristics of Trials Analyzed in Systematic Review

Article	Patients/Population	Intervention	Outcome Measures	Results
Abelson M. and Welch D., 2000	Allergic conjunctivitis. n=29.	Treatment of allergic conjunctivitis with olopatadine ophthalmic solution	Subjective itching scale measured at 3, 7, and 10 minutes.	Difference was seen in favor of Patanol at 3, 7, and 10 minutes.
Berger et al, 2006	Seasonal allergic rhinitis. Ages 12-74. n=360.	Treatment of allergic rhinitis with azelastine nasal spray.	Total nasal symptom scoring (TNSS)	Improvements in the TNSS and individual symptoms favored azelastine over cetirizine.
Charpin et al, 1995	Seasonal allergic rhinitis. Ages 12-60. n=129	Treatment of allergic rhinitis with azelastine nasal spray.	Total symptom score of the investigator (TSSI) and patient assessed visual analogue scale (VAS)	Slight overall improvement of cetirizine with TSSI but improvements seen with azelastine with VAS.
Corren et al, 2005	Seasonal allergic rhinitis. Ages 12-74. n=307	Treatment of allergic rhinitis with azelastine nasal spray.	Total nasal symptom scoring (TNSS)	Azelastine spray improved the instantaneous TNSS compared with cetirizine
Crampton, H., 2003	Eligible subjects were >18 years. Rhinoconjunctivitis. n=80	Treatment of allergic conjunctivitis with ketotifen	Redness and itching scoring on a scale of 0-4 (0 = none, 4 = severe)	Ketotifen ophthalmic solution decreased the signs and symptoms of ocular and nasal allergic rhinoconjunctivitis
Horak, et al, 2006	Seasonal allergic rhinitis. Ages 18-55. n=45	Treatment of seasonal allergic rhinitis with azelastine	Major nasal symptom score (MNSS), total nasal symptom score (TNSS)	Azelastine spray improved MNSS and TNSS compared to desloratadine
Korsgren et al, 2007	Seasonal allergic rhinitis. n=36	Treatment of seasonal allergic rhinitis with cetirizine	Total nasal symptom score (TNSS)	Cetirizine intranasal spray showed an improvement of TNSS compared to oral cetirizine

Table 3 | Overall Total Nasal Symptom Scoring

Study	Scoring Method	Topical Antihistamine/Overall symptom score or percentage decrease	Oral Antihistamine/Overall symptom score or percentage decrease
Berger et al	Total Nasal Symptom Score	Azelastine Nasal Spray/ 24.2% decrease in nasal symptoms	Cetirizine/ 19.2% decrease in nasal symptoms
Charpin et al	Total Symptom Score of the Investigator.	Azelastine Nasal Spray/ 61% decrease in nasal symptoms	Cetirizine/ 67% decrease in nasal symptoms
Corren et al	Total Nasal Symptom Score	Azelastine Nasal Spray/ 29.3% decrease in nasal symptoms	Cetirizine/ 23.0% decrease in nasal symptoms
Horak et al	Major Nasal Symptom Score	Azelastine Nasal Spray/ 2.1 reduction in the overall mean score	Desloratadine/ 1.2 reduction in the overall mean score
Korsgren et al	Total Nasal Symptom Score	Intranasal cetirizine/ 3.76 overall mean total symptom score	Oral cetirizine/ 3.25 overall mean total symptom score

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