Antihistamine: A Useful Medication with Minimal Adverse Drug Reactions to Improve Acne Symptoms and Reduce Sebum Production

Lorraine Wang
Pacific University

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Antihistamine: A Useful Medication with Minimal Adverse Drug Reactions to Improve Acne Symptoms and Reduce Sebum Production

Abstract

Background: Acne vulgaris is a common skin disease that affects not only teenagers but also the general population. Although acne is not physically disabling, its psychological impact can be striking, contributing to low self-esteem, depression, and anxiety. As a result, there is a significant demand for effective acne therapies. Antihistamine is a widely used medication to treat several allergic skin conditions and yet it also has been found to decrease complications of acne and improve acne symptoms. For the severe cystic acne vulgaris, oral retinoids such as isotretinoin is the primary treatment; however, health care providers hesitate to prescribe isotretinoin due to its adverse drug reactions. On the other hand, antihistamine is well known by its safe and minimal side effects. Can an antihistamine intervention in standardized treatment of acne vulgaris significantly impact the improvement of acne symptoms and reduce sebum production?

Methods: An exhaustive search was conducted by MEDLINE-OVID, CINAHL, UptoDate, Web of Science, Google scholar, MEDLINE-PubMed, Clinicalkey, and ProQuest by using keywords: acne vulgaris and antihistamine. Relevant articles were assessed for quality using GRADE.

Results: After the exhaustive search, two studies met the inclusion criteria and eligibility criteria. Effect of antihistamine as an adjuvant treatment of isotretinoin in acne: a randomized, controlled comparative study contains the comparison of 20 patients with moderate acne are treated with isotretinoin and another 20 patients with moderate acne are treated with additional antihistamine. Identification of Histamine Receptors and Reduction of Squalene Levels by an Antihistamine in Sebocytes was conducted on human tissue to verify the decrease of sebum production by the antihistamine’s effect.

Conclusion: Both studies demonstrate the usefulness of an histamine antagonist in reducing sebum production and improving acne symptoms. Due to its low cost and safety, a recommendation can be made for antihistamine to treat acne vulgaris as an adjuvant therapy to standardized treatment.

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Capstone Project

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First Advisor
David Keene PA-C

Keywords
Acne vulgaris, antihistamine

Subject Categories
Medicine and Health Sciences

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Antihistamine: A Useful Medication with Minimal Adverse Drug Reactions to Improve Acne Symptoms and Reduce Sebum Production

Lorraine C.F. Wang

A Clinical Graduate Project Submitted to the Faculty of the
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Pacific University
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For the Masters of Science Degree, Aug 8th, 2015

Faculty Advisor: Annjanette Sommers, PA-C, MS
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
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Keywords: Acne vulgaris, antihistamine
Acknowledgements

[Redacted for privacy]
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List of Abbreviations

GAGS……………………………………………………….Global Acne Grading System
DPH..........................................................................................................Diphenhydramine
RT-PCR…………………………………Reverse transcription polymerase chain reaction
SD……………………………………………………………………...Standard Deviation
Antihistamine: A Useful Medication with Minimal Adverse Drug Reactions to Improve Acne Symptoms and Reduce Sebum Production

BACKGROUND

Acne Vulgaris is one of the most common cutaneous disorders worldwide affecting any age or race group. The reported prevalence of acne varies from 35% to over 90% of adolescents at some stage; moreover, a significant number of patients continue to experience acne or develop new-onset acne after the teenaged years.\textsuperscript{1,2} There are abundant resources mentioning antihistamine treatment as adjuvant therapy to resolve complications of acne vulgaris such as itchiness, urticaria and edema, and some resources even mention its effectiveness in reducing inflammation and preventing scar formation. Although acne is not physically disabling, its psychological impact can be striking, contributing to low self-esteem, depression, and anxiety.\textsuperscript{3-5} As a result, there is a significant demand for effective acne therapies. Current treatment of acne vulgaris includes topical and oral antibiotics, hormonal therapy, antiseptic medication and retinoids.\textsuperscript{6}

For the severe cystic acne vulgaris, oral retinoids such as isotretinoin are considered the most effective treatment\textsuperscript{7,8}; however, health care providers hesitate to prescribe isotretinoin due to its adverse drug reactions.\textsuperscript{9,10} On the other hand, antihistamine is well known by its safety and minimal side effects. During an immune reaction, the inflammatory mediator, histamine, is release into the local environment by mast cell and basophils.\textsuperscript{11} Immunologic reaction to \textit{Propionibacterium acne}, the causative organism of acne vulgaris, and subsequent histamine-mediated inflammatory damage to keratinocytes has been discovered.\textsuperscript{12} In addition, mast cell induced fibrosis in skin and elsewhere in the body can complicate acneic lesions by scar formation and can be
prevented by antihistamines if administered in time.\textsuperscript{13, 14} Possible presence of
dermographism such as subclinical urticarial and facial edema in a large number of acne
patients could be successfully controlled by provision of antihistamines due to its effect
on allergic reactions.\textsuperscript{15} With the role that histamine and sebum production may play in
acne pathophysiology, can antihistamine treatment be useful in the management of acne
vulgaris?

METHODS

An exhaustive search of available medical literature was conducted using
Medline-OVID, CINAHL, UptoDate, and Web of Science, Google scholar, MEDLINE-
PubMed, Clinicalkey, and ProQuest by using keywords: acne vulgaris and antihistamine.
The studies are selected if they were published in the English language, conducted on
humans or human tissues, published during 2008 or later. They also needed to include a
comparison of treatment with and without antihistamines to see if antihistamines reduce
sebum production on human tissue and improves acne symptoms clinically.
Bibliographies and relevant articles were further researched for sources. Relevant articles
were assessed for quality using the Grading of Recommendations, Assessment,
Development and Evaluation (GRADE) \textsuperscript{16}.

RESULTS

After the exhaustive search, the initial result yielded 18 articles for review of
relevancy. Two studies met the eligibility criteria including one randomized controlled
Lee et al

The randomized controlled trial\textsuperscript{16} sought after the effects of antihistamine as an adjuvant treatment of isotretinoin in acne including non-inflammatory lesion count, inflammatory lesion count, total lesion count, GAGS score and patient satisfaction. Furthermore, sebum excretion and erythema index were measured along the clinical trial. Acne flare and side effects are also included as a result. It was designed as a 12-week study with blinded assessment of data collectors and three independent dermatologists. Forty Korean patients with moderate to severe acne symptoms were enrolled and divided evenly into two groups (see Table 2). The control group was treated with isotretinoin only (20 mg per day, approximately 0.2–0.4 mg/kg per day); and the treatment group was treated with combination therapy of isotretinoin and antihistamine, desloratadine (5 mg per day). No other acne treatments besides a washing and moisturizing procedure were allowed. Patients with other systemic diseases, concurrent use of other acne therapies, other dermatological conditions requiring interfering treatment were excluded as subjects. Women who were pregnant, nursing, or planning a pregnancy were excluded due to possible hormonal influences. The patients were assessed at the beginning of treatment and at 2, 4, 8 and 12 weeks after treatment. T-test and P value were assessed for significant differences between two groups at each visit as statistical analysis.\textsuperscript{17}

The primary outcome was clinical acne symptoms improvement including acne lesion counts, severity by GAGS score, and patient satisfaction. Non-inflammatory lesion counts and inflammatory lesion counts started to show a significant difference at week 2.
(P<0.05) and the mean non-inflammatory lesion counts in the treatment group reduced to 17.8% whereas there is a remaining of 44.8% lesion counts in the control group. Correspondingly, inflammatory lesion counts indicate a reduction of 22.9% in the treatment group and 55.8% in the control group; likewise, a significant difference of total lesion counts was also demonstrated in the 12 weeks of treatment (P<0.001 at week 12). According to GAGS score, statistically significant differences were found starting at week 4 between the two groups (P<0.05), and it is consistent in percentage with reduction of lesion counts from baseline. There were 50% of patients that improved on GAGS score and no patients worsened in the treatment group; conversely, 40% of patients improved on GAGS score and 10% of patients worsened in the control group comparing to the baseline. Patient satisfactions showed a mean ± standard deviation score of 2.75 ±0.18 in control group and 3.4 ±0.15 in treated group on a 4-point scale. 

Secondary outcomes included skin sebum excretion, erythema measurement, acne flare, and side effects. Both sebum excretion (µg/cm²) and erythema score (arbitrary unit) declined in the control group and the treatment group; however, a statistical significant difference was found between the two groups started from week 4 in the case of sebum excretion while the significant difference between the two groups started from week 2 in the case of erythema scores. In the speaking of acne flares, six patients in the control group were evident whereas only one patient in the treatment group experience acne flare during the 12-week treatment. Common side effects in both groups include cheilitis, xerosis, itchiness, sting, and burning sensation etc. Although both groups tolerated treatment generally well, the treatment group showed even better tolerability with minimal side effects.
The authors stated the main limitation of the study is that follow-up evaluation was not performed after the 12-week clinical trial; therefore, studies with larger sample size and longer follow-up period are needed to support the new treatment approach. In addition, the authors recommended further studies evaluating the efficacy of antihistamines as a single therapeutic method as well as a maintenance therapy after achieving remission of disease using isotretinoin.

**Pelle et al**

In this observational study, the authors wanted to identifying histamine receptors and reduction of squalene levels by an antihistamine in human sebocytes to further extend in acne treatment. Sebocytes are the major cells of the sebaceous gland and are responsible for producing sebum. Reducing sebum production minimizes the blockage of pores to curtail during an episode of acne growth. The cell cultures were obtained as SZ95 sebocytes, an immortalized sebocyte cell line, from Dr. C Zouboulis in frozen ampoules. Total RNA was isolated from sebocytes using a High Pure RNA Isolation Kit to extract RNA from sebocytes by reverse-transcriptase-polymerase chain reaction (RT-PCR) analysis. Immunofluorescence technique was then used to dye and verify the existence of histamine receptors in sebocytes and sebaceous gland. The authors also extract squalene as a biomarker, which is a major component of human sebocytes, from sebocytes to measure its response to 50µM diphenhydramine (DPH) and 100µM diphenhydramine. In addition, an experiment was designed to determine the reduction of squalene level was not a cytotoxic event caused by diphenhydramine.

Primary outcomes include the presence of histamine receptor in human sebocytes, DPH reduces squalene level in sebocyte and proof for the fact that DPH is not cytotoxic.
H-1 histamine receptors were clearly identified on RNA extracted from SZ95 sebocytes by agarose gel electrophoresis RT-PCR analysis. H-2 receptors were either not detected or only slightly discovered during the experiment. They assigned $1 \times 10^6$ cells each in the control group and two experiment groups with 50µm DPH and 100µm DPH. Squalene standards were used to calculate the amount of squalene in the samples (nmol): 6.27 ±0.73 SD in control group; 2.37 ±0.24 SD in 50µm DPH group; 2.03 ±0.97 SD in 100µm DPH group. (n=4, P<0.08 in 50µm DPH; P<0.03 in 100µm DPH group, using a two-tailed, Student’s t-test assuming unequal variances). There was no significant cell decrease between the control group and the experiment groups when testing on the cytotoxicity of DPH after approximately a 16 hour-exposure revealed its non-cytotoxicity. 18

There were no limitations stated by the authors; however, they strongly encouraged measurements of cAMP levels in sebocytes treated with DPH to be the important next step in elucidating the mechanism.

**DISCUSSION**

The prescription of H-1 antagonist is helpful in reducing sebum production due to histamine receptors found on human sebocytes and decreased squalene level by using DPH, a commonly used H-1 antagonist worldwide. 18 In addition, clinical improvement on both the GAGS score and patient satisfaction demonstrate antihistamine should be included as adjuvant medication in standardized treatment of acne vulgaris. 17 Health care providers should be encouraged to prescribe antihistamine to the general population
affected by acne vulgaris, especially since antihistamines like diphenhydramine have an established safety profile.

The systematic review was able to discuss the two studies\textsuperscript{17,18} that provides evidence and supports the usefulness of antihistamine in treating acne patients; nevertheless, both studies have limitations.

In Lee et al,\textsuperscript{17} sample size of a total 40 patients was legitimate yet relatively small. Although the process of selecting patients was not explained, it stated it is a randomized, controlled comparative study. The authors stated the blinding process included group assignment to examiners and blinding three different dermatologists as data collectors when assessing each visit of the 40 patients; however, it was not possible to blind the patients and providers that prescribed isotretinoin and desloratadine. All the 40 patients were assessed at the beginning of the clinical trial using GAGS score and revealed there was no significant difference in the control and the treatment group at baseline. At each visit of week 2, 4, 8 and 12, GAGS score was again measured and it was consistent to acne lesions count. There was no withdrawal in this study; therefore, the attrition bias was avoided. The study was the very first randomized controlled clinical trial, and being published in Dec. 2014, it is the most current study available on the topic. A larger sample size with longer period of following up and relapsing of acne vulgaris after treatment could further extended to support this new treatment approach. If antihistamine is useful in reducing sebum production and improving the symptoms of acne vulgaris, clinicians may be able to try an antihistamine, which may lower the number of patients who would need more aggressive treatment such as isotretinoin. In fact the use of
antihistamines may even reduce the dosage of isotretinoin to minimize its side effect. Moreover, antihistamine could be the treatment of choice as maintenance therapy. This could be a new clinical question requiring further research.

The manner in which the Pelle et al study\textsuperscript{18} was conducted on human tissue in a histological manner without clinical proof on actual acne patients would be an important limitation to consider. Furthermore, all cells obtained in the experiment are from one female doctor, which led to selection bias as another limitation. There was no blinding level mentioned since it is an observational study; otherwise, the results were consistent with other aspects of the study. Squalene was used as a biomarker to measure sebum production in human sebocytes; however, it is not considered surrogate outcome since it is the major component of sebum, and reducing sebum production is an important clinical question regarding acne vulgaris. It is strongly suggested by the authors that further studies should be conducted on the mechanism of antihistamine reducing sebum production. In addition, to explore different types of histamine receptors and antihistamine in more detail would be even better to direct health care providers on prescribing medications for acne patients.

There was one clinical study\textsuperscript{19} worth mentioning which was conducted in 1979. The study measured sebum excretion rate on forehead skin before and at intervals during 1-6 weeks of treatment with cimetidine, an H-2 histamine antagonist, (1 g/day in divided doses) in four male and six female patients with acne. The decrease of sebum excretion was statistically significant started at week 2 and was still apparent at 5 weeks. Due to the lack of control group, the comparison was made between patients before antihistamine
treatment and completion of 6 weeks treatment of cimetidine. However, H-2 histamine receptors were not commonly found on human sebocytes according to Pelle et al\textsuperscript{18}; moreover, the authors of this study stated that they were not sure whether the effect of reducing sebum production came from the blockage of histamine receptors or antiandrogenic effect of cimetidine itself. This past study and the more recent studies show the variety of research that has been and still needs to be done to understand how antihistamine relates to acne.

Acne vulgaris is a broad category that concludes different types of acne presentation. Moreover, antihistamine is also a broad category concludes all histamine receptors antagonist. Although further studies need to be conducted to direct health care providers on prescribing antihistamine, the two studies including in this systematic review recommend that health care providers embrace H-1 antihistamine as part of standardized treatment for acne patients. It is the new treatment approach in which benefits outweigh harms compared to use isotretinoin alone for moderate to severe acne symptoms.

CONCLUSION

Antihistamines have demonstrated its usefulness in managing acne vulgaris and it should be added as adjuvant treatment on treating acne patients. Despite the severity of acne vulgaris, antihistamine will be useful on sebum secretion and its minimal side effects are most likely tolerable in all kinds of patients. There may be benefits of prescribing antihistamines to patients which need to be evaluated: first reducing or avoiding isotretinoin in order to minimize adverse drug reactions, secondly antihistamine
has effects on preventing subclinical itching, urticarial, and facial edema, and third its anti-inflammatory effect could possibly lower the chances of scar forming and improve clinical redness and other symptoms. Moreover, the cost of antihistamine is affordable and accepted by the general population. As a result, a recommendation can be made to health care providers in adding antihistamine as part of standardized treatment in acne patients, even though further randomized controlled studies designed to evaluate the effect on clinical improvement are needed.
References


Table 1. GRADE Quality of Assessment

<table>
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<tr>
<th>Quality Assessment</th>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
<th>Importance</th>
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<tr>
<td>Clinical Improvement of Acne Symptoms</td>
<td>1</td>
<td>1 RCT</td>
<td>No serious limitation</td>
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<td>Critical</td>
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<td>Reduction of Sebum Production</td>
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<td>1 RCT</td>
<td>Serious limitation</td>
<td>No serious indirectness</td>
<td>Very serious imprecision</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Very Low</td>
<td>Important</td>
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a Small sample size  
b Only one study measuring this outcome  
c Pelle et al contains all cells only from one female doctor
Summary of Findings

Table 2. Lee et al
Baseline demographic and clinical characteristics of acne patients

<table>
<thead>
<tr>
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<th>Isotretinoin (Control)</th>
<th>Isotretinoin + Desloratadine (Treatment)</th>
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<td>Female</td>
<td>12</td>
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</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age (years, mean±SD)</td>
<td>21.9±2.1</td>
<td>21±3.7</td>
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<tr>
<td>Duration (years, mean±SD)</td>
<td>4.8±2.76</td>
<td>4.6±2.99</td>
</tr>
<tr>
<td>Dosage of isotretinoin (mg/kg per day, mean±SD)</td>
<td>0.31±0.05</td>
<td>0.29±0.03</td>
</tr>
<tr>
<td>Non-inflammatory</td>
<td>43.6±19.4</td>
<td>41.5±17.7</td>
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<tr>
<td>Inflammatory</td>
<td>30±15.5</td>
<td>30.6±17</td>
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<tr>
<td>Total</td>
<td>73.7±27.7</td>
<td>72±14.9</td>
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<td>GAGS (score, mean±SD)</td>
<td>27.2±6.09</td>
<td>28.2±6.48</td>
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Table 3. Lee et al
Changes in assessment with time and difference between both groups

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<tr>
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<td>Baseline</td>
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<td>Baseline</td>
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<tr>
<td>Non-inflammatory</td>
<td>100%</td>
<td>44.8%</td>
<td>100%</td>
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<tr>
<td>Inflammatory</td>
<td>100%</td>
<td>55.8%</td>
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<td>GAGS</td>
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<tr>
<td>Patient Satisfaction</td>
<td>Slightly satisfied</td>
<td>Satisfied</td>
<td>Very satisfied</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>9 (45%)</td>
<td>7 (35%)</td>
<td>4 (20%)</td>
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<tr>
<td>Mean±SD (4-point scale)</td>
<td>2.75±0.18</td>
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<td>3.4±0.15</td>
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<tr>
<td>Sebum Production</td>
<td>Significant difference started at Week 4 (P=0.005)</td>
<td></td>
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<tr>
<td>Erythema Index</td>
<td>Significant difference started at Week 2 (P=0.02)</td>
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### Table 4. Pelle et al
DPH reduces squalene in sebocytes

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<tr>
<th></th>
<th>Control</th>
<th>50µM DPH</th>
<th>100µM DPH</th>
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<td>1× 10^6</td>
<td>1× 10^6</td>
<td>1× 10^6</td>
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<td>Squalene Level that represent Sebum Production (nmol, mean±SD)</td>
<td>6.27±0.73</td>
<td>2.37±0.24</td>
<td>2.03±0.97</td>
<td>P&lt;0.08 in 50µM DPH</td>
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<td>P&lt;0.03 in 100µM DPH</td>
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