An Evidence-Based Review of the Efficacy of Antihistamines in Relieving Pruritus in Atopic Dermatitis

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Objective: To critically review the body of clinical trials that refute or support the efficacy of antihistamines in relieving pruritus in patients with atopic dermatitis.

Design: Review of MEDLINE from 1966 through March 1999, the Cochrane Database of Systematic Reviews, and Best Evidence to identify therapeutic trials of antihistamines in patients with atopic dermatitis.

Main Outcome Measures: All randomized controlled trials or clinical trials of antihistamines used in the treatment of atopic dermatitis. We found 16 studies throughout the literature.

Results: Large, randomized, double-blind, placebo-controlled clinical trials with definitive conclusions (grade A trials) have not been performed. Two grade B trials (small, rigorous, randomized trials with uncertain results due to moderate to high α or β error) refuted the use of antihistamines in relieving pruritus. One grade B trial supported the efficacy of antihistamines in relieving pruritus. All remaining trials (grade C) lacked placebo controls or randomization, or contained fewer than 20 patients in each treatment group.

Conclusions: Although antihistamines are often used in the treatment of atopic dermatitis, little objective evidence exists to demonstrate relief of pruritus. The majority of trials are flawed in terms of the sample size or study design. Based on the literature alone, the efficacy of antihistamines remains to be adequately investigated. Anecdotally, sedating antihistamines have sometimes been useful by virtue of their soporific effect and bedtime use may be warranted. There is no evidence to support the effectiveness of expensive nonsedating agents.

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Atopic dermatitis is a common chronic or relapsing eczematous dermatitis characterized by intense pruritus and occurring primarily in infants and children with a personal or family history of atopy. Nine percent to 12% of all children are affected with atopic dermatitis, and 60% to 70% of those with mild to severe dermatitis will continue to experience symptoms into adulthood. A significant proportion of patients who have outgrown the typical manifestations of the disease develop irritant dermatitis, which may be chronic and work-disabling, especially in the context of wet, dirty, or caustic conditions.

Pruritus is one of the most common symptoms of atopic dermatitis. The itch-scratch cycle exacerbates damage to the epidermal barrier thereby increasing water loss and drying, which creates a suitable environment for skin pathogens to cause infection and flaring of symptoms. Despite the frequent use of histamine H1 receptor antihistamines in managing pruritus in atopic dermatitis, few randomized, double-blind, placebo-controlled clinical studies have evaluated efficacy. In addition to older sedating formulations, expensive nonsedating agents are sometimes used in the absence of any clinical evidence that demonstrates relief of pruritus.

RESULTS

Sixteen studies have evaluated the efficacy of antihistamines in relieving pruritus in patients with atopic dermatitis. Large, randomized, double-blind, placebo-controlled clinical trials with definitive conclusions have not been performed (grade A trials). Two grade B trials refute the use of antihistamines in relieving pruritus and 1 grade B trial supports the efficacy of antihistamines. Four grade C trials refute and 9 grade C trials support the antipruritic effects of antihistamines. These results are summarized in the
METHODOLOGY

We searched the MEDLINE database for trials of antihistamines published from 1966 through March 1999. The search used the keywords dermatitis, atopic/therapy or eczematotherapy and histamine H1 antagonists/therapy with publication types randomized controlled trial or clinical trial. The Cochrane Database of Systematic Reviews and Best Evidence databases were also searched using the keywords atopic dermatitis and eczema. The quality of each trial was ranked by applying a modified version of Sackett’s criteria for clinical evidence. Grade A trials are large, randomized, double-blind, placebo-controlled studies with low false-positive (α) and low false-negative (β) errors. Grade A trials lead to definitive conclusions with precise point estimates of treatment effect. Grade B studies are also randomized, double-blind, placebo-controlled studies, but include a small number of patients, thereby increasing the likelihood of high false-positive and/or false-negative errors. Grade B results may be statistically significant, for example, yet provide an imprecise point estimate of treatment effects. Grade C trials lack 1 or more of the following criteria: randomization, placebo control, or blinding. Trials with fewer than 20 patients in each treatment group are also grade C trials. Case reports and case series are categorized as grade C trials.

Table. The grade B studies present the best evidence available and are discussed below.

Berth-Jones and Graham-Brown conducted a randomized, double-blind, placebo-controlled, crossover study of 28 subjects given 120 mg of terfenadine twice daily for 1 week. The mean age and fulfillment of the diagnostic criteria of Hanifin and Rajka were noted, but the characteristics of the study subjects and their disease severity were not provided. Of the 28 subjects, 4 were excluded from the analysis due to failure to comply with the protocol either by altering their topical steroid treatment or by failing to take the trial medications as directed. The degree to which these dropout patients differed in terms of disease severity from the remaining subjects was not provided. The subjects were permitted to use topical steroids and emollients to maintain their dermatitis in a stable condition. The type of topical steroid and the quantity used by each subject were not noted. The first 3 days of the study were a washout period, and assessment was performed only during the last 4 days of each treatment. Subjects used visual analog scales to record the severity of pruritus. Subjects were also examined by investigators at the end of each treatment period and the severity of excoriation was evaluated. The mean (±SE) visual analog scores for terfenadine and placebo were 23.95 (±4.9) and 25.13 (±5.1), respectively. The authors concluded that terfenadine was not effective in relieving pruritus. However, the 95% confidence intervals of the means of the visual analog scores were ±41% of the value of the point estimates, limiting the precision of the study. Because of the small number of subjects and the imprecision of the point estimate of pruritus relief, a treatment effect cannot be ruled out.

Wahlgren et al performed a randomized, double-blind, placebo-controlled, crossover study of terfenadine, 60 mg twice daily, and clemastine fumarate, 2 mg twice for 3 days with intervening 4-day washout periods. The study was randomized with a double-dummy protocol, with each patient receiving 3 courses in random order: (1) active terfenadine and placebo clemastine fumarate; (2) placebo terfenadine and active clemastine fumarate; and (3) placebo terfenadine and placebo clemastine fumarate. Twenty-five adults fulfilling the criteria of Hanifin and Rajka were enrolled in the study. Age, sex, disease duration, and history of atopy were provided. Patients were permitted to use topical hydrocortisone and emollients during the study. The quantity of topical hydrocortisone used during the 4-day washout period after each treatment course was comparable between groups. Patients recorded pruritus using visual analog scales and a computerized method for self-recording. The authors found no significant difference in the intensity of itch between the 3 treatment groups using either assessment method. The sedative effect of clemastine fumarate was significantly greater than terfenadine or placebo, yet its antipruritic effect did not differ.

Hannukela et al conducted a randomized, double-blind, placebo-controlled, parallel study of cetirizine hydrochloride, a nonsedating antihistamine, at 10 mg, 20 mg, or 40 mg taken once daily for 4 weeks. The study included 178 adults, patient characteristics, such as mean age, sex, weight, and prior use of emollients and hydrocortisone were provided. All groups were comparable at baseline. The criteria of Hanifin and Rajka were not used in patient selection. Of the 178 patients, 51 were excluded from the statistical analysis of efficacy: adverse reactions (20), noncompliance (19), protocol violations (5), use of a forbidden drug (5), lost to follow-up (1), and did not fulfill the inclusion criteria (1). The authors neither revealed the characteristics and extent of disease in these dropout patients nor did they address the potential effects of their exclusion. The active group included 26, 34, and 35 patients who received 10 mg, 20 mg, and 40 mg of cetirizine hydrochloride daily for 4 weeks, respectively. The placebo group had 32 subjects. Patients used emollients and hydrocortisone cream during the study and the containers were weighed before and after the trial. Pruritus was assessed using visual analog scales by both investigators and patients. At the end of the trial, the investigators’ pruritus scores of the active and placebo groups at all doses were significantly decreased compared with baseline values. However, none of the active groups showed a statistically significant improvement compared with the placebo group. The patients’ pruritus scores at the final visit showed that the active and placebo groups had a statistically significant improvement from baseline values (P ≤ .001). Only the group receiving the 40-mg dose showed a statistically significant improvement compared with placebo (P ≤ .05). The authors conceded that a 40-mg dose is sedating, and the improvement in pruritus was linked to a soporific ef-
fect. This finding suggests that nonsedating antihistamines are most useful at soporific doses, thereby calling into question the utility of the nonsedating formulation.

COMMENT

Antihistamines are a standard therapy in atopic dermatitis and are recommended in many clinical treatment protocols. Despite frequent use, surprisingly few clinical studies have examined their efficacy. Of the 16 trials found in the literature, none fulfill the criteria for a well-designed study that also includes a sufficient number of subjects to permit definitive conclusions. The largest study group contains 35 patients, which is not sufficient to yield a precise estimate of treatment effect.

Sedating antihistamines are frequently used, especially at bedtime, to facilitate peaceful sleep. Because itch intensity often increases at night, the soporific effect of sedating formulations can be quite useful. Daytime use, however, is problematic, although some patients may acclimate to this effect. The development of nonsedating formulations (eg, loratadine) has led physicians to prescribe these agents in the hope of providing daytime relief. Studies have failed to demonstrate efficacy yet some physicians are prescribing them for patients. Moreover, compared with sedating agents, they are many times more expensive.

Diphenhydramine hydrochloride is frequently prescribed for patients with atopic dermatitis. The average wholesale price per 25-mg tablet of generic diphenhydramine hydrochloride equals $0.04 (1998 dollars).

### A Review of Clinical Trials Evaluating the Efficacy of Antihistamines in the Treatment of Atopic Dermatitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Grade†</th>
<th>Antihistamines</th>
<th>Treatment Group‡</th>
<th>Placebo Group</th>
<th>Completing Study</th>
<th>Double-blind Randomized</th>
<th>Placebo-Controlled Crossover</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berth-Jones and Graham-Brown7</td>
<td>B</td>
<td>Terfenadine</td>
<td>24</td>
<td>24</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wahlgren et al⁸</td>
<td>B</td>
<td>Terfenadine</td>
<td>25</td>
<td>25</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Frosch et al¹⁰</td>
<td>C</td>
<td>Chlorpheniramine plus cimetidine hydrochloride</td>
<td>16</td>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Savin et al¹¹</td>
<td>C</td>
<td>Loratadine</td>
<td>10</td>
<td>10</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Foulds and MacKie¹²</td>
<td>C</td>
<td>Cimetidine hydrochloride</td>
<td>20</td>
<td>NA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Krause and Shuster¹³</td>
<td>C</td>
<td>Astemizole</td>
<td>6</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

### Support Efficacy of Antihistamines

- **Hannukela et al³⁰**: B Cetirizine hydrochloride, mg 10 20 30 35 32 127 Yes Yes Yes No
- **Langeland et al¹⁴**: C Loratadine 16 16 16 16 16 Yes Yes Yes No
- **Doherty et al³¹**: C Acrivastine 13 13 13 13 13 Yes Yes Yes No
- **LaRosa et al³⁶**: C Cetirizine hydrochloride 12 12 12 12 12 Yes Yes Yes No
- **Monroe¹⁷**: C Loratadine 14 14 14 14 14 Yes Yes Yes No
- **Behrendt and Ring⁰**: C Cetirizine hydrochloride 0.7 0.7 0.7 0.7 0.7 Yes Yes Yes No
- **Simons et al³⁰**: C Hydroxyzine hydrochloride, mg/kg 0.7 0.7 0.7 0.7 0.7 Yes Yes Yes No
- **Klein and Galare⁰**: C Hydroxyzine hydrochloride 0.7 0.7 0.7 0.7 0.7 Yes Yes Yes No
- **Yoshida et al³³**: C Clemastine fumarate 123 123 123 123 123 No Yes No No
- **Nuovo et al³⁲**: C Chlorpheniramine 1 1 1 1 1 Yes Yes Yes No

*NA indicates not applicable. †The quality of each trial was ranked by applying a modified version of Sackett’s criteria for technical evidence. Grade A studies are large, randomized, double-blind, and placebo-controlled studies with low false-positive and false-negative error rates that show definitive conclusions with precise point estimates of treatment effect; none of the studies in the Table met the grade A criteria. Grade B studies are randomized, double-blind, and placebo-controlled studies with small sample sizes, high false-positive and/or false-negative error rates; the results may be statistically significant yet provide an imprecise point estimate of treatment effects. Grade C studies lack 1 or more of the following: randomization, placebo control, or blinding. These studies have a small sample size (~20) and include case reports and case studies. ‡In crossover studies, all patients received both the trial medication and the placebo. §Ketotifen is not an antihistamine.
approximately $2.14 (1998 dollars)\textsuperscript{24} and a 1-month supply for 1 daily dosage equals $64, approximately 27 times more expensive than over-the-counter diphenhydramine hydrochloride. The newer nonsedating agents have no proven clinical efficacy and their associated costs are substantial, especially in a patient population with a chronic disease. This is not to say that patients should use sedating agents either. They are similarly not proved in relieving pruritus.

Should antihistamines be used in the treatment of atopic dermatitis? Because some early studies\textsuperscript{23,25} reported increased histamine levels in normal and lesional eczematous skin and because the pruritic action of intradermal histamine can be clinically suppressed with H\textsubscript{1} receptor antagonists, it was assumed that antihistamines could be useful in the treatment of atopic dermatitis. Moreover, the efficacy of antihistamines in other dermatologic disorders, such as chronic urticaria, has contributed to their application in atopic dermatitis. However, clinical trials of antihistamines have been inadequate in terms of study design and sample size, and the outcomes are contradictory. Current recommendations and practices are based largely on the individual experiences of patients and physicians.

Again, sedating antihistamines are anecdotaly useful in relieving pruritus at night by their soporific effect. Accordingly, we prescribe them at bedtime to help patients sleep. Do nonsedating agents have a role as well? No objective evidence exists to support the effectiveness of nonsedating antihistamines in treating atopic dermatitis. Clinical studies have failed to demonstrate a clear benefit or have attributed a decrease in pruritus to sedative effects at high doses. In patients with comorbid conditions, such as allergic rhinitis, allergic conjunctivitis, allergen-induced asthma, and chronic urticaria, nonsedating agents may be useful.

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REFERENCES