A Double Blind Trial of $H_1$ and $H_2$ Receptor Antagonists in the Treatment of Atopic Dermatitis

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Summary. Eighteen patients with atopic dermatitis were randomly chosen for a clinical trial to compare the action of the $H_2$ receptor antagonist cimetidine in combination with the $H_1$ receptor antagonist chlorpheniramine against chlorpheniramine alone and against placebo. Each treatment period lasted for 4 weeks. Intensity of pruritus was recorded daily by the patient on an analogue scale. Global clinical assessment was graded on a 5-point scale every 2 weeks by the investigators and weekly by the patient himself. Further study parameters were: quantity of the corticosteroid ointment used for 'emergencies', immunoglobulin E level, and eosinophil count. The data of 16 patients was evaluated. There was no significant difference in any of the study parameters during the three treatment periods. On the basis of this study, the combined administration of $H_1$ and $H_2$ receptor antagonists is of no benefit in the treatment of atopic dermatitis.

Key words: Atopic dermatitis — Pruritus — Treatment — Cimetidine — Chlorpheniramin

Introduction

A main feature of atopic dermatitis is the pruritus which in most patients cannot be sufficiently controlled by the administration of classic $H_1$ histamine receptor antagonists. As $H_2$ receptor sites have been demonstrated in the skin and its vasculature (Marks and Greaves 1977; Greaves et al. 1977) it is possible that $H_2$ receptor antagonists may also be of therapeutic value in this dermatological disorder. Although the exact pathogenesis of pruritus and the eczematous lesions is still unclear, there is some evidence that the concentration of histamine is increased in the skin (Johnson et al. 1960) and in the plasma (Ring et al. 1978) of patients with atopic dermatitis.

The object of this study was to block the effect of histamine in patients with atopic dermatitis by using an $H_1$ antagonist alone and in combination with an $H_2$ antagonist and to record any changes in their clinical state, particularly regarding the pruritus.

Materials and Methods

Materials

1. Cimetidine 200g tablets for oral administration. 2. Chlorpheniramine 4 mg tablets for oral administration. 3. Placebo tablets identical with 1. 4. Placebo tablets identical with 2. The coded materials were supplied by Smith, Kline and Dauelsberg (Göttingen, FRG).

Patients

Eighteen patients were admitted to the study, but two of them dropped out for personal reasons. Sixteen patients (13 females, 3 males), aged between 14 and 43 years, with a history of atopic dermatitis for at least 3 years completed the study.

Exclusion criteria were: 1. Treatment with systemic corticosteroids or ACTH within the last two months; 2. Change of topical medication in the last month; 3. History of very distinct seasonal variations in their atopic dermatitis; 4. Presence of any nonatopic dermatitis related pathological finding, detected by routine laboratory screening; 5. Pregnancy or lactation.

Methods

In double blind study was conducted according to the provisions of the Declaration of Helsinki and the principles of the Bundesarzneimittelgesetz (§§ 40 and 41 AMG). The patients were informed about the nature of the study and their consent obtained. Prior to entry into the trial the patients were fully examined, the severity of their atopic dermatitis determined, and blood and urine samples taken for routine laboratory screening (see below).

The patients were allowed to use at will a bland greasey ointment which did not contain an antiinflammatory active substance (e.g. vaseline or eucerin). They also received weighed containers of 0.1% betamethasone ointment (Betnesol-V ointment, Glaxo, Ware,
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Table 1. Mean itch values (measured on 100 mm analogue scales, 0 = no itch, 100 = extreme itch)

<table>
<thead>
<tr>
<th></th>
<th>Day itch</th>
<th></th>
<th>Night itch</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cimetidine + chlorpheniramine</td>
<td>Chlorpheniramine</td>
<td>Placebo</td>
<td>Cimetidine + chlorpheniramine</td>
</tr>
<tr>
<td>Week 2</td>
<td>39.6</td>
<td>36.4</td>
<td>39.7</td>
<td>37.9</td>
</tr>
<tr>
<td>Week 3</td>
<td>34.2</td>
<td>38.3</td>
<td>40.1</td>
<td>30.5</td>
</tr>
<tr>
<td>Week 4</td>
<td>32.6</td>
<td>37.3</td>
<td>38.8</td>
<td>29.6</td>
</tr>
</tbody>
</table>

Hertfordshire, England). Any other dermatologically active medication was discontinued for the duration of the study. After 1 week the patients were re-examined and then allocated according to a randomisation list to one of the following three treatment groups:
1. Cimetidine active + chlorpheniramine active;
2. Cimetidine placebo + chlorpheniramine active;
3. Cimetidine placebo + chlorpheniramine placebo.

Each treatment period lasted 4 weeks. Following the initial treatment period the patients were subsequently allocated to the next treatment and then to the final treatment according to the randomisation list. Thus, the duration of the study was 13 weeks for each patient. The randomisation was conducted according to a latin square design. The medication was given according to the following dosage schemes:

Cimetidine (200 mg Tablets) and Chlorpheniramine Placebo. The adult patients received two tablets three times a day after meals and two tablets at bedtime (1,600 mg/day). The 14-year-old girl took two tablets after breakfast and at bedtime and one tablet after lunch and dinner (1,200 mg/day). The 15-year-old girl received the adult dosage because of her body weight of 59 kg.

Chlorpheniramine (4 mg Tablets) and Cimetidine Placebo. The adult patients received one tablet three times a day after meals and one tablet at bedtime (16 mg/day). The 14-year-old girl took one tablet after breakfast and at bedtime and one tablet after lunch. The 15-year-old girl received the adult dosage because of her body weight of 59 kg.

Assessment

Clinical visits were made at the beginning of the study, at the start of the treatment after the 1 week run-in-phase, and then every 2 weeks. Routine laboratory investigations were performed at the initial visit as well as at the end of each treatment period.

The patients received diary cards to record the following:

1. Itch. Day- and night-time itch was quantitated daily using a 100 mm analogue scale.

2. Global Assessment. Every 7 days during the study the patients recorded their change in general condition over that week. Their global assessments were expressed as much worse/worse/unchanged/better/much better.

   At each visit the following was assessed by the investigator:
   a) Distribution of the affected body area as percentage of body surface, by help of body charts.
   b) Lichenification, measured on a 4-point scale as none/mild/moderate/severe.
   c) Impetiginisation, also measured as none/mild/moderate/severe.
   d) Global assessment of change in condition since last visit, assessed by means of a 5-point scale (much worse/worse/unchanged/better/much better).
   e) Use of betamethasone ointment. Assessment was made by weighing the containers returned by the patients (at each visit the patient received a new weighed container).

Laboratory Tests. The following laboratory values were determined at the initial visit and after each treatment period: Hemoglobin, erythrocyte sedimentation rate (ESR), white blood cell count, eosinophil count, thrombocytes, serum alkaline phosphatase, total bilirubin, SGP, SGPT, LDH, urea, creatinine, and urinalysis for protein and glucose. Total IgE levels were measured by radiimmune competitive binding assay (Prist, Pharmacia, Freiburg, FRG).

Results

Sixteen patients, aged between 14 and 43 years (mean 23 years) completed the trial (Table 1). Thirteen were females, aged between 14 and 43 years (mean 22 years), and three were males, aged 17, 18 and 40 years. Duration of their disease ranged from 3 to 40 years (mean 17 years). Seven patients suffered from atopic dermatitis since birth or early childhood. In four patients manifestation of the disease first presented between 3 and 5 years of age.

Day-time and night-time itch were recorded daily by the patients using two 100 mm analogue scales. Zero represented no itch and 100 extreme itch. The data analysed represent the means of the assessments for weeks 2, 3 and 4 (Table 1). Week 1 was not included as it may have been influenced by previous treatment. With the cimetidine and chlorpheniramine the arithmetically lowest means for both day and night itch for weeks 3 and 4 were recorded. However, analysis of these results compared to the other treatment groups (Friedman's test) failed to show any significant difference.

All patients made global assessments of their general conditions at weekly intervals. Condition was recorded as much worse (−2), worse (−1), unchanged (0), better (1) or much better (2) than the previous assessment. An overall value representing the trend in general condition for each patient was obtained by summing the scores for weeks 1 to 4. The results were therefore on a scale of −8 to +8 where −8 represented rapid deterioration, +8 represented rapid improvement and 0 represented no overall change. Because of the absence of wash-out periods between treatments