A STUDY OF AN ANTIHISTAMINE WITH DELAYED ACTION IN THE TREATMENT OF PRURITIC DERMATOSES

A REPORT ON 50 CASES

by R. JOHANNY.

When considering the great many experimental investigations which have been conducted on synthetic antihistamines, against the studies of their clinical effects in men, one is surprised at the relatively small number of the latter. Yet these clinical studies generally demonstrate the slight efficacy of these compounds with respect to the inhibition of the histamine production. Besides the part played by histamine as the trigger factor in various allergic dermatoses and namely in eczema is now strongly questioned.

Nevertheless the use of antihistamines for the treatment of dermatological complaints has been a valuable advance in therapy; indeed the treatment of allergic dermatoses used to be very disappointing when one kept resorting to such uncertain methods as the determination of the allergens and the desensitization therapy. As a matter of fact the allergens are tremendously numerous and when the responsible agent has been identified after a toiling search, there is nothing that can prevent the patient to be sensitized again towards one or several other allergens.

If the antihistamines are unable to inhibit the production of histamine, everything happens as if the organism become insensible to the increase of the histamine concentration whereby the local reactional symptoms appear to be suppressed.

As shown by Duperrat's investigations, at the level of the skin, the contact with the allergen produces a chronic spasm of the arterioles, an abrupt dilatation of the capillaries, a significant increase of the capillary permeability, an edematous transudation and an acidification of the focus which leads to a fibrinoid necrosis of the local collagen; thereafter a migration
of the leukocytes and mainly of the eosinophils occurs. These various stages are reversible, except when the necrotic process has already taken place. All these symptoms, which are attended by edema, bring about a compression of the thin nervous terminals in the skin and cause therefore necessarily the itching to appear.

As to the mode of action of the antihistamines, we know at present that they prevent the capillary permeability from increasing under the influence of histamine. Consequently, the plasmatic exudation, the local edema and the pruritus do not appear any more.

Our interest for the antihistaminic agents was mainly concerned with the possibility of relieving the pruritus. The itching, which can be so distressing for the patient, is not only a subjective symptom wherefrom the patient wants to be relieved, but also, because of the scratching lesions it provokes, a true causative agent of secondary dermatoses, while it aggravates and fosters the primary dermatosis. Its suppression should thus be the first target to be aimed at by a dermatologist.

With the antihistamines we have now a powerful weapon and we must know it thoroughly to handle it properly.

A great many chemical compounds with an antihistaminic action are now available to the practitioner. They may be roughly divided into three groups:

1) the derivatives of phenhydramine, which are fairly effective but have stimulating effects;

2) the compounds of the promethazine type, which are very effective, but also strongly hypnogenetic;

3) the most recently developed compounds which are slightly stimulating, slightly hypnogenetic and slightly effective, if at all.

In the face of this problem, the physician, who is more or less satisfied with the drugs he uses, tends to get tired of the so-called novelties and to reject in advance every new drug. Such a position would not be correct because, on the one hand, it underestimates the possibilities offered by chemical synthesis and disdains the investigators' expectations to fill the gap still left open by the antihistaminic therapy. On the other hand, it would be most regrettable to mix up with the many, often uninteresting novelties, a substance which would really yield something new.
In 1949 already the American Medical Association had defined the problem and deemed it advisable to delimit the field of further research by laying down the requirements to be fulfilled for the approval of any antihistaminic agent:

1°) a longer duration of action;
2°) a lower incidence of side-effects;
3°) a larger field of action, i.e. a favourable influence upon those symptoms which did not respond satisfactorily to the existing antihistamines.

Such a compound should thus possess the following qualities:

Experimentally, it should be
- less toxic
- very potent
- longer acting

Clinically, it should
- be tasteless in order to avoid the necessity of coating and thus enhance the rapidity of its absorption;
- develop the four main actions of a good antihistamine and thus be effective against spasms, edema, pruritus and nausea.

With respect to tolerance, it should not
- induce nervous symptoms such as drowsiness, dizziness, torpor, obnubilation, stimulation;
- cause such digestive reactions as gastric irritation, vomiting, intestinal disorders;
- provoke blood disorders such as e.g. alterations in the hemogram.

Eventually it should have a long duration of action which ought to be confirmed by the test of the histaminic dermal node and the rotating chair test (labyrinthic action); clinically it should remain effective for at least 24 hours.

We have been given the opportunity to test in our department a new antihistamine recently developed and known as Buclizine hydrochloride or UCB 4445 compound, which has been marketed under the name of LONGIFENE.
We have especially studied its antipruritic action in dermatoses wherein the itching is a main factor.

Study of the antipruritic action:

Number of cases treated and supervised: 50
Age limits: 4 months and 72 years
Average ages: from 12 to 42 years

Distribution with respect to sex: 23 female and 27 male.

Dosage forms used: LONGIFENE syrup containing 5 mg of buclizine hydrochloride per teaspoonful.
LONGIFENE tablets containing each 25 mg of buclizine hydrochloride.

Dosage scheme: 2 tablets at night after dinner;
1 tablet in the morning after breakfast and, if needed;
1 tablet at noon after lunch.

When needed (and this occurred rarely) the morning dose was doubled.

We have also considered the side-effects which have been carefully noted whenever they occurred.

The results of our observations are summarized in the following table

(see page 5)
DISTRIBUTION WITH RESPECT TO THE CONDITIONS TREATED

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of cases</th>
<th>Complete relief from itching</th>
<th>Improvement of more than 50%</th>
<th>Improvement of 10 to 50%</th>
<th>Improvement up to 10%</th>
<th>No improvement</th>
<th>Average daily dose (in mg)</th>
<th>Shortest duration of the treatment (in days)</th>
<th>Longest duration of the treatment (in days)</th>
<th>Average duration of the treatment (in days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strophulus pruriginosus</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>15m</td>
<td>3</td>
<td>12</td>
<td>5</td>
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<tr>
<td>Infantile constitutional eczema</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>25m</td>
<td>5</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Acute weeping eczema</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>75m</td>
<td>5</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Chronic eczema</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>75m</td>
<td>7</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Lichenified eczema</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>125m</td>
<td>10</td>
<td>40</td>
<td>21</td>
</tr>
<tr>
<td>Neurodermatitis</td>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>125m</td>
<td>12</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>75m</td>
<td>10</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>Atypical lichenoid parapsoriasis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>100m</td>
<td>-</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>125m</td>
<td>15</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Inguinal mycosis</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>75m</td>
<td>4</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Pruritus ani vel vulvae</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>100m</td>
<td>12</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>50</strong></td>
<td><strong>14</strong></td>
<td><strong>15</strong></td>
<td><strong>12</strong></td>
<td><strong>7</strong></td>
<td><strong>2</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

SUMMARY

THE ACTION OF LONGIFENE UPON PRURITUS (as percentages)

<table>
<thead>
<tr>
<th>Complete relief</th>
<th>Improvement of more than 50%</th>
<th>Improvement of 10 to 50%</th>
<th>Improvement up to 10%</th>
<th>No Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>30</td>
<td>24</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>
The major pruritic dermatoses (neurodermatitis, lichenified eczema, lichen planus) requested as a rule 4 to 5 tablets daily, viz. 2 in the morning, 1 at noon and 2 at night to obtain a good relief of the itching.

In the acute pruritic dermatoses, the pruritus yielded to smaller doses amounting generally to 1 tablet in the morning and 2 at night.

The infantile pruritic conditions responded particularly well to the action of LONGIFENE. Yet in half of the cases of constitutional eczema the dose of one teaspoonful of syrup for every year of age appeared to be insufficient. When we increased progressively the quantity of syrup, we had no failure as regards the relief from itching and we observed no appreciable side-effect. The doses did never exceed two teaspoonfuls for every year of age. For the children over 6 years we prescribed the tablets as for adults, but of course the doses were reduced in proportion to the age of the patients.

We had two failures in this series: the first case was an old, very nervous woman who suffered since eight years from a large neurodermite in the neck and whose pruritus was relieved by surface radiotherapy. The second case was also a woman who suffered from a diffuse lichenified eczema of the lower limbs. All the antihistamines available to us (6 different specialties) proved to be ineffective in this case and we were unable to relieve the itching with large doses of a neuroplegic agent (chlorpromazine) administered both intramuscularly and orally.

UCB 4445 had no influence upon the very dermatological lesions. A few patients were selected for controls and received no external active treatment for several days during which they were only treated with daily intakes of the antihistamine: neither the elemental lesions nor the clinical evolution of the dermatosis were influenced.

Nevertheless as the complete or partial relief from the itching suppressed the scratching lesions, the duration of the disease was shortened and above all the latter was much better tolerated by the patient. This factor of relaxation or easing, which is of prime importance in all pruritic conditions, was found in all our patients who were treated with UCB 4445. We did not conduct any particular hematological controls in these cases, but the many routine examinations performed on our patients did not demonstrate any alteration of the blood count, of the differential blood count or of the hemoglobin contents.
In the 50 cases supervised we have never observed any side-reaction which could be ascribed to the drug. Yet two infants (1 strophulus, 1 constitutional eczema) exhibited some drowsiness when the doses were increased in order to relieve the itching. The adult patients were all able to continue their normal occupations during the treatment. Symptoms of digestive (nausea, gastralgia) or general intolerance (dizziness, drowsiness, mental obnubilation) have never been noted.

In this connection and although it was not included in our experiment let us mention the case of a diplomat who had eaten some lobster at a formal reception after which he developed an urticaria which appeared mainly in the morning. This urticaria was most inconvenient because he had to attend a congress on that day and he could not decently scratch himself in public. He called at a physician who prescribed an antihistamine. The itching was suppressed and so was surprisingly a speech of our unfortunate diplomat because he was completely obnubilated and unable to deliver his speech. The physician prescribed than a stimulating and euphorizing antihistamine; the diplomat was able to make his speech but scratched himself fiercely with his free hand. The diplomat took then our advice and we prescribed 2 tablets of Buclizine hydrochloride at night and 1 in the morning. On the next day our diplomat had to make a speech again. This time he was able to deliver it while holding his paper with both hands.

As a conclusion from our trial we may state that the UCB 4445 compound deserves to be ranked among the best antipruritic agents available to us for the management of dermatological complaints and should be considered as an item of daily prescription because of its absence of side-effects and long duration of action.