**Antihistamines in the treatment of asthma**

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Antihistamines, which block histamine at the H<sub>1</sub>-receptor level, have been used for the treatment of allergic and nonallergic rhinitis, conjunctivitis and skin diseases, in which histamine has been shown to play an important role.

In asthma, the use of antihistamines is still under investigation. Not only do some investigators deny that antihistamines are beneficial [Schuller [1]], but they might even be harmful. Based on a very small number of asthmatic children, who apparently deteriorated during treatment with a drug possessing both an H<sub>1</sub>-blocking activity and anticholinergic properties, their report lead to the contraindication of these drugs in asthma in the US. However, a Position Paper issued by the American Academy of Allergy and Immunology [2] proposed that the drugs are safe and may be used in the treatment of asthma. The efficacy of antihistamines in asthma needs to be reconsidered, as new drugs largely devoid of side-effects have been available for the past 10 yrs [3-5].

**Points in favour of a role of antihistamines in asthma**

**Histamine plays a role in the pathogenesis of asthma**

Histamine plays a role in the mechanisms of asthma [6]. It is released during the early and late phase allergic reactions following bronchial challenge with allergen [7]; mast cells are present in the biopsies of allergic and nonallergic asthmatics [8] and histamine levels are increased in the bronchoalveolar lavage (BAL) fluid of asthmatics [9]. Moreover, a significant correlation has been demonstrated between non-specific bronchial hyperreactivity and histamine levels in BAL fluid [9]. Histamine can induce the secretion of mucus by bronchial glands, cause extravasation of plasma proteins leading to airways mucosal oedema, contract the airway smooth muscle [6] and may play a role in the immunomodulation of the immunoglobulin E (IgE) immune response [10], as well as in the regulation of the airway inflammation by the activation of epithelial cells and macrophages and possibly by inducing smooth muscle hyperplasia.

The inhalation of histamine induces a bronchoconstrictive response in most subjects, but asthmatic patients are hyperreactive to histamine [11].

**Antihistamines possess some "anti-allergic" properties**

Antihistamines block histamine at its H<sub>1</sub>-receptor level but many drugs possess other properties that may be relevant for their efficacy [12]. Loratadine and terfenadine reduce, in a dose-dependent manner, the release of eicosanoids from human dispersed lung cells and reduce the release of histamine and prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) during nasal challenge with allergen. After allergen challenge, cetirizine decreases the eosinophil influx into the skin but it is not yet clear if it has the same effect on nasal and bronchial cells. Although the exact significance of these properties is still not fully understood, they might be involved in asthma.
Links between asthma and rhinitis

Many patients with allergic rhinitis present both rhinitis and asthma. Many patients with allergic rhinitis alone have an increased nonspecific bronchial hyperreactivity [13]. Finally, sinusitis is thought to be a causative factor in asthma [14]. Although the exact links between the nose and the lung are far from understood, it has been proposed that the treatment of the nasal symptoms may improve asthma.

Points against a role of antihistamines in asthma

Histamine is only one of the mediators of asthma and does not explain chronic inflammation of the airways

Histamine is one of the mediators of "allergic" and/or "asthmatic" inflammation. It is likely to play a role in the spasmogenic phase of asthma but its importance in chronic inflammation of the airways remains to be determined. Moreover, mast cells and basophils are not the only cell types involved in airways inflammation in asthma [15] and many other cells, mediators, toxic metabolites, cytokines and growth factors appear to be more important than histamine and/or metachromatic cells. Finally, asthma is not only an inflammatory disease but remodels the airways inducing permanent abnormalities [16]. Thus, it appears that antihistamines may only be partly effective in the treatment of chronic asthma and poorly effective in either long-standing asthma or in the most severe patients.

Anti-allergic drugs are usually poorly effective in the treatment of severe asthma

Sodium cromoglycate appears to be more effective in young asthmatics and in patients with mild asthma. It is usually less effective in the treatment of severe asthmatics [17]. The results obtained with ketotifen are less consistent but similar conclusions may be drawn [18].

Clinical relevance of antihistamines in asthma

Bronchodilating activity of antihistamines

The bronchodilating activity of a single dose of antihistamine was reported in the early 1980s [19] and confirmed in some but not all studies [20-26]. Many studies found a significant difference between the bronchodilating activity of the placebo and the active drug, but they do not appear to be clinically relevant, since differences are usually small. In studies showing a significant effect of antihistamines, there was no dose-response effect [26]. Long-term studies specifically examining this bronchodilating effect are lacking and long-term clinical studies of antihistamines in asthma suggest that this activity disappears after one or two weeks.

Thus, the bronchodilating activity of antihistamines may be limited in intensity and duration and, with our current knowledge, it does not support their use in asthma.

Provocative challenges

Exercise and cold air challenges. Several studies have been performed to assess the protective effect of antihistamines in exercise-induced asthma and related challenges such as nebulized water, hypertonic saline or cold air (table 1) [27-40]. Many of these studies show that antihistamines result in significant protection, but in some studies the effect, although significant, is very small and does not appear to be clinically relevant. Moreover, in such situations, calcium antagonists and α-blockers were found to be effective in the laboratory but had little or no effect when they were administered to patients in an attempt to improve asthma.

Allergen challenge. Many studies have also been performed in allergic asthmatics in order to prove the efficacy of antihistamines during the early and late phase allergic reactions. However, there have been discrepancies in the results published. Terfenadine [41, 42] and astemizole [43], but not loratadine [44] and cetirizine [45], have been shown to reduce the early phase allergic reactions. However, there have been discrepancies in the results published. Terfenadine [41, 42] and astemizole [43], but not loratadine [44] and cetirizine [45], have been shown to reduce the early phase reaction, but even with terfenadine the response was usually small and varied considerably between subjects.

Studies attempting to demonstrate an effect on the late phase reaction have been carried out on a very small number of patients and results are highly variable [46-48]. At best, the effect is again small. It is, therefore, impossible to ascribe any clinically relevant protective effect of antihistamines on the late phase reaction.

Nonspecific airway challenge. Nonspecific bronchial hyperreactivity is a cardinal feature of asthma and drugs such as inhaled corticosteroids and, to a lesser extent, nedocromil sodium or sodium cromoglycate have been found to reduce the magnitude of histamine and/or methacholine inhalation challenge. Histamine challenge has no value for testing the effect of antihistamines on nonspecific bronchial hyperreactivity depending on the intrinsic activity of the drugs. Studies performed using methacholine challenge did not show any difference before and after treatment although it may be argued that the duration of the studies was too short to observe any significant effect [49-51]. Antihistamines can block challenge with adenosine [52] or platelet-activating factor (PAF) [53] but the clinical relevance of such challenges needs to be characterized.
ANTIHISTAMINES IN ASTHMA TREATMENT

Clinical studies

Only studies performed during seasonal or perennial asthma make it possible to assess the value of antihistamines in the treatment of asthma. Many inconclusive studies in both seasonal and perennial asthma have been performed but never published and this represents a major gap in our knowledge of the efficacy of antihistamines in asthma.

Seasonal asthma

Difficulties in designing the studies. There are several drawbacks in the studies examining the effects of antihistamines in the treatment of seasonal asthma.

Seasonal asthma is mainly caused by pollens and the major symptoms of pollinosis are usually related to rhinoconjunctivitis, with asthma occurring in the most severe cases. There have been a number of trials performed in which no treatment for the nose or eyes was administered and, as a result, most of the placebo-treated patients dropped out of the study [54-55]. Nasal and ocular symptoms should be treated during any asthma trial with drugs not affecting the interpretation of the study.

There is no commonly accepted treatment for nasal or ocular symptoms during asthma trials and the choice depends on many parameters: topical or oral drugs; all patients treated identically [56] or only patients who require a treatment for severe symptoms; treatment applied during the whole trial or only during the peak of the season.

Administration of the antihistamine may start before the season in a prophylactic treatment or very soon after the patients develop asthma. It is critical that long-standing asthmatics should be excluded from such studies since antihistamines are likely to have maximal effect on patients who have a low degree of bronchial inflammation.

Inclusion criteria are not standardized but it is commonly accepted that patients should present a reversibility of the airway obstruction after the inhalation of β₂-agonists. However, in grass pollen asthma, few patients have a reversible airways obstruction of >15% of forced expiratory volume in one second (FEV₁).

The grass pollen season lasts 6-8 weeks in most countries but it is highly heterogeneous, pollen counts varying daily and from year to year. The tree pollen season (birch primarily) is shorter, usually intense in terms of pollen counts and symptoms, but highly variable from year to year. The ragweed pollen season is the most constant in terms of onset, peak and duration but it lasts only 4-6 weeks. It is, therefore, difficult to propose crossover trials with washout periods between treatments.

The analysis of the data is not easy. All trials examine symptom and medication scores, some evaluate the evolution of the pulmonary function tests or peak flow rates. However, in grass pollen asthma mean peak flow rates usually show little decrease of this interesting parameter. There is no study of nonspecific bronchial hyperreactivity available.

Results of double-blind studies with control or placebo groups. Table 2 summarizes the results of the controlled studies performed with cetirizine and terfenadine in seasonal asthma [54-62]. It must be pointed out that the doses of antihistamines were always greater than those administered for rhinoconjunctivitis and, in the study of RAPFERT ET AL. [60] the dose was 4.5 fold greater than recommended. If this increased dose is to become the recommended dose for asthma, the short- and long-term safety of the drug should be monitored in specific studies.

In two studies, the patients received no treatment for rhinitis and most of those under placebo dropped out from the study. These studies cannot be analysed further since it is unclear whether the patients dropped out because of nasal or bronchial symptoms [55, 59].

Table 1. — Effect of antihistamines in exercise challenge and related challenges

<table>
<thead>
<tr>
<th>First author</th>
<th>Ref.</th>
<th>Drug</th>
<th>Dose mg</th>
<th>Duration</th>
<th>n</th>
<th>Group of patients</th>
<th>Challenge</th>
<th>p</th>
<th>Clinical relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azevedo [27]</td>
<td>T</td>
<td>180</td>
<td>1 dose</td>
<td>30</td>
<td></td>
<td>Children</td>
<td>Exercise</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Backer [28]</td>
<td>A</td>
<td>30</td>
<td>1 dose</td>
<td>20</td>
<td></td>
<td>Adult</td>
<td>Hyperventilation in cold air</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Badger [29]</td>
<td>T</td>
<td>120</td>
<td>1 dose</td>
<td>11</td>
<td></td>
<td>Adult</td>
<td>Exercise</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Barberio [30]</td>
<td>T</td>
<td>Variable</td>
<td>1 dose</td>
<td>14</td>
<td></td>
<td>Children</td>
<td>Exercise</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Bertra [31]</td>
<td>T</td>
<td>240</td>
<td>1 dose</td>
<td>12</td>
<td></td>
<td>?</td>
<td>Cold air</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Clee [32]</td>
<td>A</td>
<td>10</td>
<td>1 dose</td>
<td>9</td>
<td></td>
<td>19-33 yrs</td>
<td>Exercise</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Finney [33]</td>
<td>T</td>
<td>180</td>
<td>1 dose</td>
<td>9</td>
<td></td>
<td>21-40 yrs</td>
<td>Exercise</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Finney [34]</td>
<td>T</td>
<td>180</td>
<td>1 dose</td>
<td>9</td>
<td></td>
<td>21-40 yrs</td>
<td>Exercise</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Ghosh [35]</td>
<td>T</td>
<td>180</td>
<td>1 dose</td>
<td>12</td>
<td></td>
<td>Adults</td>
<td>Nonisotonic aerosol</td>
<td>0.02</td>
<td>Yes</td>
</tr>
<tr>
<td>Gong [36]</td>
<td>C</td>
<td>10</td>
<td>1 dose</td>
<td>12</td>
<td></td>
<td>Adults</td>
<td>Exercise</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Hopp [37]</td>
<td>T</td>
<td>240</td>
<td>1 dose</td>
<td>12</td>
<td></td>
<td>19-42 yrs</td>
<td>UNDW</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>O'Hickey [39]</td>
<td>T</td>
<td>120</td>
<td>2 doses</td>
<td>10</td>
<td></td>
<td>Adults</td>
<td>Hypertonic saline</td>
<td>0.02</td>
<td>Yes</td>
</tr>
<tr>
<td>Patel [40]</td>
<td>T</td>
<td>180</td>
<td>1 dose</td>
<td>10</td>
<td></td>
<td>15-50 yrs</td>
<td>Exercise</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

UNDW: ultrasonized distilled water; T: terfenadine; A: astemizole; C: cetirizine; NS: nonsignificant; *: when recalculated.
Controlled washout period is critical. The study may be performed in parallel groups. Run-in period is critical, since asthma is highly variable. The study may be performed in parallel groups or in a cross-over manner but in the latter case the washout period is critical.

Difficulties in designing the studies. There are also several drawbacks in the studies examining the effects of antihistamines in the treatment of perennial asthma [28, 57, 60–62]. The design of the trial is critical. Asthma is a chronic inflammatory disease leading to a remodelling of the airways. It is, therefore, suggested that antihistamines will be more effective in patients with mild asthma and in the younger asthmatics. In perennial asthma, rhinitis and conjunctivitis are not always severe and nasal or ocular treatments are not required by most patients. Anti-inflammatory drugs should be carefully avoided for a long period of time, since it is unlikely that antihistamines will add significant benefit to inhaled corticosteroids. The duration of the run-in period is critical, since asthma is highly variable. The study may be performed in parallel groups or in a cross-over manner but in the latter case the washout period is critical.

Table 2. Controlled studies examining the efficacy of oral antihistamines in the treatment of asthma

<table>
<thead>
<tr>
<th>First author</th>
<th>Ref.</th>
<th>Drug</th>
<th>Dose mg</th>
<th>Duration n</th>
<th>Age yrs</th>
<th>Study design</th>
<th>Asthma</th>
<th>Stat. sign.</th>
<th>Clinical relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bousquet</td>
<td>[28]</td>
<td>A</td>
<td>20 o.d.</td>
<td>22 days</td>
<td>20</td>
<td>DB-PC-CO</td>
<td>Chronic</td>
<td>ns</td>
<td>Yes</td>
</tr>
<tr>
<td>Bousquet</td>
<td>[54]</td>
<td>C</td>
<td>10, 15 b.i.d.</td>
<td>14 days</td>
<td>80</td>
<td>DP-PG*</td>
<td>Pollen</td>
<td>s</td>
<td>Minimal</td>
</tr>
<tr>
<td>Britman</td>
<td>[55]</td>
<td>C</td>
<td>15 o.d.</td>
<td>14 days</td>
<td>57</td>
<td>DB-PC-PG</td>
<td>Pollen</td>
<td>s</td>
<td>Too many drop outs</td>
</tr>
<tr>
<td>Dirkman</td>
<td>[56]</td>
<td>C</td>
<td>10 b.i.d.</td>
<td>6 weeks</td>
<td>43</td>
<td>DB-PG*</td>
<td>Pollen</td>
<td>s</td>
<td>Yes</td>
</tr>
<tr>
<td>Duksen</td>
<td>[57]</td>
<td>L</td>
<td>10 o.d.</td>
<td>8 weeks</td>
<td>17</td>
<td>DB-PC-CO</td>
<td>Chronic</td>
<td>ns</td>
<td>Yes</td>
</tr>
<tr>
<td>Kurzeja</td>
<td>[58]</td>
<td>C</td>
<td>10 b.i.d.</td>
<td>?</td>
<td>20</td>
<td>DB-PG*</td>
<td>Birch pollen</td>
<td>s</td>
<td>?</td>
</tr>
<tr>
<td>Pedrali</td>
<td>[59]</td>
<td>C</td>
<td>10 b.i.d.</td>
<td>28 days</td>
<td>60</td>
<td>DB-PG*</td>
<td>Pollen</td>
<td>s</td>
<td>Too many drop outs</td>
</tr>
<tr>
<td>Rafferty</td>
<td>[60]</td>
<td>T</td>
<td>180 t.i.d.</td>
<td>4 weeks</td>
<td>18</td>
<td>34.7±5.6</td>
<td>DB-PC-CO</td>
<td>Pollen</td>
<td>s</td>
</tr>
<tr>
<td>TAYTARD</td>
<td>[61]</td>
<td>T</td>
<td>120 b.i.d.</td>
<td>2 weeks</td>
<td>46</td>
<td>12–53</td>
<td>DB-PC-CO</td>
<td>Mite</td>
<td>s</td>
</tr>
<tr>
<td>Teale</td>
<td>[62]</td>
<td>T</td>
<td>120</td>
<td>1 dose</td>
<td>8</td>
<td>29–72</td>
<td>DB-PC</td>
<td>Nocturnal</td>
<td>s</td>
</tr>
</tbody>
</table>

A: astemizole; C: cetirizine; L: loratadine; T: terfenadine; DB: double-blind; PC: placebo-controlled; CO: cross-over; PG: parallel group; Stat. sign.: statistical significance; ns: nonsignificant; s: significant. *: the control group received T 60 mg b.i.d. to control nasal and ocular symptoms.

In other studies, patients received either cetirizine (20 or 30 mg daily) or a rescue medication given to all patients in the control group, terfenadine, at a dose that was suggested to be ineffective in asthma (60 mg b.i.d.). The results of the study of Bousquet et al. [54] are not very convincing, possibly because the control group was under terfenadine. Finally, there are only two studies published in detail showing some efficacy of antihistamines in asthma [56, 60]. However, not all parameters were improved and the pulmonary function, peak flow rates or β2-agonist rescue medication were similar in the treated and placebo groups.

These studies show a moderate effect of antihistamines in the treatment of seasonal asthma but, since many inconclusive studies have not been published, more data are needed before a firm conclusion can be reached.

Perennial asthma

Difficulties in designing the studies. There are also several drawbacks in the studies examining the effects of antihistamines in the treatment of perennial asthma [28, 57, 60–62]. The design of the trial is critical. Asthma is a chronic inflammatory disease leading to a remodelling of the airways. It is, therefore, suggested that antihistamines will be more effective in patients with mild asthma and in the younger asthmatics. In perennial asthma, rhinitis and conjunctivitis are not always severe and nasal or ocular treatments are not required by most patients. Anti-inflammatory drugs should be carefully avoided for a long period of time, since it is unlikely that antihistamines will add significant benefit to inhaled corticosteroids. The duration of the run-in period is critical, since asthma is highly variable. The study may be performed in parallel groups or in a cross-over manner but in the latter case the washout period is critical.

Results of double-blind studies with control group. The study of TAYTARD et al. [61] is the only published study showing a favourable effect of antihistamines in chronic symptoms of perennial asthma. Using terfenadine at a dose of 120 mg b.i.d. in a cross-over study carried out in mild asthmatics, they observed that when patients were treated with the antihistamine they presented significantly less symptoms, needed significantly less β2-agonists and presented an improvement in pulmonary function as assessed by FEV1 and peak flow rates. However, the improvement in pulmonary function was small and may have little clinical relevance. Many other inconclusive studies have been performed but never published.

Indications for antihistamines in asthma

The indications for antihistamines in the treatment of asthma are still vague and more data are needed before a firm conclusion can be drawn. New studies are needed to compare the efficacy of antihistamines with accepted anti-asthma treatment.

References
Histamine and Bronchodilator action of the Early Terfenadine
Effect of terfenadine and ipratropium bromide on Therapy for airway inflammation in Asthma.
Terfenadine is a potent and selective H1-receptor antagonist. It inhibits the release of histamine from mast cells and basophils. In vivo, terfenadine increases the time to a 50% fall in forced expiratory volume in 1 second (FEV1) after exercise challenge.


