Use of antihistamines in pediatrics

A del Cuvillo,1 J Sastre,2 J Montoro,3 I Jáuregui,4 M Ferrer,5 I Dávila,6 J Bartra,7 J Mullol,8 A Valero,7

1 Clínica Dr. Lobatón, Cádiz, Spain
2 Service of Allergy, Fundación Jiménez Díaz, Madrid, Spain
3 Allergy Unit, Hospital La Plana, Villarreal (Castellón), Spain
4 Service of Allergy, Hospital de Basurto, Bilbao, Spain
5 Department of Allergology, Clínica Universitaria de Navarra, Pamplona, Spain
6 Service of Immunoallergy, Hospital Clínico, Salamanca, Spain
7 Allergy Unit. Service of Pneumology and Respiratory Allergy, Hospital Clínic (ICT), Barcelona, Spain
8 Rhinology Unit, ENT Service (ICEMEQ), Hospital Clínic, Barcelona, Spain

Summary

Drugs with antihistamine action are among the most commonly prescribed medicines in pediatrics. According to the International Medical Statistics (IMS), almost two million antihistamine units (in solution) for pediatric use were sold in Spain during 2006 - at a cost of nearly 6 million euros. Of this amount, 34% corresponded to first-generation (or sedating) antihistamines.

The difficulties inherent to research for drug development increase considerably when the pediatric age range is involved. The use of any medication in this age group must adhere to the strictest safety criteria, and must offer the maximum guarantees of efficacy. For this reason, detailed knowledge of the best scientific evidence available in relation to these aspects is essential for warranting drug use.

The first-generation antihistamines have never been adequately studied for pediatric age groups, though they are still widely used in application to such patients. In contrast, studies in children have been made with the second-generation antihistamines, allowing us to know their safety profile, and such medicines are available at pediatric dosages that have been well documented from the pharmacological perspective.

The present review affords an update to our most recent knowledge on antihistamine use in children, based on the best scientific evidence available.


Resumen

Los medicamentos con acción antihistamínica son uno de los grupos terapéuticos más usados en pediatría. En España, según datos de IMS, se vendieron en 2006 cerca de dos millones de unidades de antihistamínicos (en solución) para uso pediátrico, lo que supuso un gasto de casi 6 millones de euros. De este montante un 34% fueron antihistamínicos de primera generación o sedativos.

Las dificultades propias de la investigación para el desarrollo de fármacos se incrementan mucho cuando se trata de edades pediátricas. El uso de cualquier fármacon en este grupo de edades debe argumentarse siguiendo los criterios más estrictos de seguridad y con las máximas garantías de eficacia. Por este motivo, el conocimiento detallado de las mejores pruebas científicas disponibles en estos aspectos es fundamental para respaldar su uso.

Los antihistamínicos de primera generación no han sido nunca correctamente estudiados para los grupos de edades pediátricas y sin embargo, siguen siendo muy utilizados. Los antihistamínicos de segunda generación sí han aportado estudios en niños que permiten conocer su perfil de seguridad, y están disponibles en dosificaciones pediátricas bien documentadas desde el punto de vista farmacológico.

En esta revisión se pretende realizar una actualización del conocimiento más reciente en cuanto al uso de antihistamínicos en niños, a través de un enfoque basado en las mejores pruebas científicas disponibles.

Introduction

Drugs with antihistamine action are among the most commonly prescribed medicines in pediatrics. According to the data obtained by the Alergológica 2005 study [1], of the Spanish Society of Allergology and Clinical Immunology, 56.4% of all pediatric patients (under age 14 years) in the study had received some antihistamine prior to visiting the allergologist. Of these, 22% corresponded to first-generation antihistamines. According to the International Medical Statistics (IMS), almost two million antihistamine units (in solution) for pediatric use were sold in Spain during 2006 - at a cost of nearly 6 million euros. Of this amount, 34% corresponded to first-generation (or sedating) antihistamines.

The difficulties inherent to research for drug development increase considerably when the pediatric age range is involved. The use of any medication in this age group must adhere to the strictest safety criteria, and must offer the maximum guarantees of efficacy. For this reason, detailed knowledge of the best scientific evidence available in relation to these aspects is essential for warranting drug use.

The European Medicines Evaluation Agency (EMEA), in its document “Guide to the clinical development of medical products for the treatment of rhinoconjunctivitis”, under the section on special considerations in pediatric patients, specifies that in children over two years of age the pharmacokinetic studies made prior to drug authorization suffice to establish the minimum effective dose - assuming that the efficacy results in adolescents/adults are also valid for children. For children under two years of age, where immune reaction is considered to be different, specific efficacy studies are required. In all the age groups the safety data are of greater importance, and studies involving one to three months of follow-up are demanded, with special attention to the adverse effects upon growth.

The first-generation antihistamines have never been adequately studied for pediatric age groups, though they are still used in an apparently high percentage of such patients. In contrast, studies in children have been made with the second-generation antihistamines, allowing us to know their safety profile, and such medicines are available at pediatric dosages that have been well documented from the pharmacological perspective.

Over five years have elapsed since the last exhaustive review based on scientific evidence was published in relation to antihistamine use in pediatrics [2], and since then new data have appeared and new scientific contributions have been made that allow us to amplify current knowledge in support of antihistamine use in pediatric patients. The present review affords an update to such knowledge on antihistamine use in children, based on the best scientific evidence available.

Pharmacological aspects of antihistamines in pediatrics

The drug pharmacokinetic and pharmacodynamic characteristics can differ greatly depending on the age group considered. These characteristics determine efficacy and particularly safety, and make it possible to predict the behavior of a given drug in the body.

Table 1 shows the most important pharmacological aspects according to the studies published on the antihistamines most widely used in pediatrics [3-23].

In general, antihistamines are well absorbed following oral administration as both solid and liquid formulations, and reach maximum plasma concentrations between 1-4 hours after dosing in both pediatric patients and in adults.

The plasma half-life depends on the drug metabolization and clearance processes within the body, and although such processes are the same in both children and in adults, they are comparatively accelerated in children in the case of certain antihistamines. As a result, ideal dosing in such cases is once every 12 hours instead of once every 24 hours (e.g., in the case of levocetirizine in kindergarten children) [18-20].

All first-generation antihistamines, as well as most second-generation drugs, are metabolized in the liver by the P450 cytochrome enzyme system. Only cetirizine, levocetirizine and fexofenadine are largely eliminated without metabolic transformation (in urine in the first two cases, and in bile in the case of fexofenadine).

There are no studies of the effects of possible drug interactions in pediatric age groups between antihistamines and P450 cytochrome inhibitors, or drugs which are metabolized via this pathway. The only exception is a study of children with chloroquine-resistant malaria, where the plasma concentrations of this drug were seen to be significantly greater, and were reached sooner, when administered in combination with chlorpheniramine [23].

The pharmacodynamic aspects, such as the onset of action and its duration, are studied both in children and in adults based on the histamine-induced skin wheal and erythema inhibition model. The last column in Table 1 reports the time intervals in which significant wheal and erythema inhibition takes place with the different antihistamines. For most of them, the time to action is within one hour, with persistence of the effect during 24 hours.

In the same way as in adults, no tachyphylaxis or tolerance of this effect on histamine-induced wheal and erythema production is observed [8].

Efficacy of antihistamines in the treatment of allergic rhinitis in children

Allergic rhinitis (hay fever) is the most frequent chronic disorder in the pediatric population, and its prevalence is increasing [24]. It can have an important impact upon the health of the child, causing a reduction in quality of life [25], and can influence the development of associated diseases such as asthma, sinusitis or seromucosal otitis [26].

The H1 antihistamines have demonstrated their efficacy in the treatment of pediatric allergic rhinitis in many studies and in different age groups, though the methodological quality of such studies has increased considerably only in the last two decades. There are no well conducted clinical studies in children involving first-generation antihistamines; as a result, the latter should not be recommended as first line treatment.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg or mg/kg*)</th>
<th>Patients (no.)</th>
<th>Age (years)</th>
<th>Cp max (ng/ml)</th>
<th>Tmax (h)</th>
<th>T½ (h)</th>
<th>erythema/wheal (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brompheniramine</td>
<td>4</td>
<td>14</td>
<td>9.5 ± 0.4</td>
<td>7.7 ± 0.7</td>
<td>3.2 ±0.3</td>
<td>12.4 ± 1.1</td>
<td>0.5 to 36</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>0.12*</td>
<td>11</td>
<td>11 ± 3</td>
<td>13.5 ± 3.5</td>
<td>2.5 ± 1.5</td>
<td>13.1 ± 6.3</td>
<td>1 to 24</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>1.25*</td>
<td>7</td>
<td>8.9 ± 1.7</td>
<td>81.8 ± 30.2</td>
<td>1.3 ± 0.5</td>
<td>5.4 ± 1.8</td>
<td>1 to 12</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>0.7*</td>
<td>12</td>
<td>6.1 ± 4.6</td>
<td>47.4 ± 17.3</td>
<td>2.0 ± 0.9</td>
<td>7.1 ± 2.3</td>
<td>n/d</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>1 (c/12h)</td>
<td>6</td>
<td>3 ± 1</td>
<td>3.25</td>
<td>1.33</td>
<td>n/d</td>
<td>n/d</td>
</tr>
<tr>
<td><strong>Second generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine</td>
<td>5</td>
<td>10</td>
<td>8 ± 0.6</td>
<td>427.6 ± 144.2</td>
<td>1.4 ± 1.1</td>
<td>7.1 ± 1.6</td>
<td>1 to 24</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>9</td>
<td>8 ± 0.6</td>
<td>978.4 ± 340.6</td>
<td>0.8 ± 0.4</td>
<td>6.9 ± 1.6</td>
<td>0.5 to 24</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>8</td>
<td>2.7</td>
<td>560 ± 200</td>
<td>1.44 ± 1.1</td>
<td>4.9 ± 0.6</td>
<td>n/d</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>15</td>
<td>12.3 ± 5.5m</td>
<td>390 ± 135</td>
<td>2 ± 1.3</td>
<td>3.1 ± 1.8</td>
<td>n/d</td>
</tr>
<tr>
<td>Ebastine</td>
<td>5</td>
<td>10</td>
<td>7.3 ± 0.4</td>
<td>108.6 ± 11.8</td>
<td>2.8 ± 0.3</td>
<td>11.4 ± 0.7</td>
<td>0.5 to 28</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>7.8 ± 0.4</td>
<td>209.6 ± 24.2</td>
<td>3.4 ± 0.4</td>
<td>10.1 ± 1.1</td>
<td>0.5 a 28</td>
<td></td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>30 (c/12 h)</td>
<td>14</td>
<td>9.8 ± 1.8</td>
<td>178 ± 22</td>
<td>2.4 ± 0.2</td>
<td>18.3 ± 1.2</td>
<td>1 to 24</td>
</tr>
<tr>
<td></td>
<td>60 (c/12h)</td>
<td>14</td>
<td>9.8 ± 1.8</td>
<td>286 ± 34</td>
<td>2.4 ± 0.2</td>
<td>17.6 ± 1</td>
<td>1 to 24</td>
</tr>
<tr>
<td>Loratadine</td>
<td>10</td>
<td>13</td>
<td>10.6</td>
<td>4.38</td>
<td>1</td>
<td>13.79</td>
<td>1 to 12</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>18</td>
<td>3.8 ± 1.1</td>
<td>7.8</td>
<td>1.2</td>
<td>n/d</td>
<td>n/d</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>0.125* (c/12h)</td>
<td>15</td>
<td>20.7 ± 3.7m</td>
<td>286 ± 68</td>
<td>1</td>
<td>4.1 ± 0.67</td>
<td>1 to 28</td>
</tr>
<tr>
<td></td>
<td>0.18*</td>
<td>14</td>
<td>8.6 ± 0.4</td>
<td>450 ± 37</td>
<td>1.2 ± 0.2</td>
<td>5.7 ± 0.2</td>
<td>n/d</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>N 183 (76.3%)</td>
<td>58</td>
<td>&gt;6m-&lt;1</td>
<td>1-2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Pharmacological characteristics of the first- and second-generation antihistamines most commonly used in pediatric patients.
However, there is sufficient scientific evidence to recommend the use of second-generation antihistamines in the different pediatric age groups: cetirizine, levocetirizine, ebastine, fexofenadine and loratadine all have well documented clinical efficacy in children - particularly after four years of age [2,27-31]. For younger patients, studies are made fundamentally to assess safety, and less information is obtained on efficacy - due to the difficulty of conducting randomized, controlled and masked clinical trials in small children. Adults show a strong placebo effect in clinical studies of allergic rhinitis. In children, this placebo effect may be a comparatively stronger confounding factor, particularly when efficacy assessment is based on subjective parameters such as symptoms scores or days without symptoms (Figure 1). To avoid this problem, it would be advisable to base such studies on objective measures of improvement such as inflammatory markers (nasal nitric oxide, nasal cytology) or the measurement of nasal peak inspiratory flow, in order to establish dose-response correlations.

In recent years, health-related quality of life (HRQoL) has become a very important clinical variable for assessing drug efficacy, based on the use of adequately validated generic or specific questionnaires. We now have studies with solid methodological designs that assess the usefulness of antihistamines in improving the quality of life of children with allergic rhinitis (Figure 2) [29].

In the same way as in adults, antihistamines are effective in alleviating most of the symptoms of pediatric allergic rhinitis: itching, rhinorrhea, and sneezing - though they appear to be less effective against nasal congestion. There are no randomized, controlled and masked clinical trials warranting the use of formulations that mix first-generation antihistamines with nasal decongesting agents (systemic vasoconstrictors), despite the fact that they are so often used in pediatric practice. A clinical study [32] has demonstrated the efficacy (in terms of symptoms reduction) of loratadine (a second-generation antihistamine) combined with pseudoephedrine.

Likewise, no clinical studies have been published comparing the efficacy of antihistamines with that of nasal corticoids for improving nasal congestion or the rest of symptoms of allergic rhinitis in children - in contrast to the situation in adults, where such studies have been made.

**Efficacy of antihistamines in the treatment of childhood asthma**

A recent epidemiological study conducted in Spain, Alergológica 2005 [1], showed that in children under 14 years of age with bronchial asthma, antihistamine treatment was indicated in up to 30% of cases.

Histamine is an important inflammatory mediator within the respiratory tract. Following provocation by an inhaled allergen, it has been demonstrated that plasma histamine levels increase, coinciding with the immediate and late response phases of the allergic reaction. A rise in plasma histamine also has been reported during asthma attacks.
Antihistamines such as ketotifen, cetirizine and loratadine have shown a range of effects upon asthma: they reduce exercise-induced asthma attacks [33], improve cough in children with pollen allergy during the pollinic season [34], and improve asthma symptoms in children [35].

A systematic review with metaanalysis has been published on the efficacy of ketotifen as treatment alone or in combination with other drugs for the control of asthma and wheezing in children [36]. The review concluded that the scientific evidence derived from randomized controlled trials indicates that ketotifen alone or in combination with other co-interventions effectively improves asthma and wheezing control in children with mild and moderate asthma. However, due to the high proportion of atopic children in some trials, the results are not necessarily extendable to all asthmatic children. The cost of the resulting benefit comprises minor side effects such as sedation and body weight gain. The validity of this conclusion is limited by the deficient methodological quality of the trials included in the review.

According to the findings of the epidemiological study, Alergológica 2005 [1], a full 51.6% of the asthmatic children included (under 14 years of age) suffered allergic rhinitis-conjunctivitis - thus supporting the hypothesis that rhinitis and asthma form part of one same disease, on the basis of their binding characteristics: histological (respiratory epithelium), physiological (nasobronchial reflex), and pathological (immune response to aeroallergens in two phases - immediate and late). In many cases, asthmatic patients with rhinitis receive antihistamine treatment, and it has been seen that in such situations patient lung function improves significantly [37]. Likewise, scientific evidence indicates that correct management of rhinitis is associated with a significant reduction in the risk of hospital admission and/or emergency care due to asthma attacks [38].

Many studies have shown allergic rhinitis to be an independent risk factor for the development of asthma [39]. It is interesting to postulate whether correct treatment of rhinitis using antihistamines may prevent the development of asthma, or even whether the treatment of atopic dermatitis with antihistamines is able to prevent the disease. A number of clinical studies have attempted to demonstrate this possibility for ketotifen, cetirizine and loratadine - concluding that ketotifen is very useful for preventing the development of asthma in children with atopic dermatitis and high IgE levels [40]. In addition, ketotifen has been shown to be effective in preventing the development of asthma in children with a family history of respiratory allergy and high IgE levels [41], and cetirizine prevents the development of asthma in children with atopic dermatitis sensitized to aeroallergens. Moreover, such preventive effects persist for 18 months after discontinuing the treatment (Figure 3) [42]. In turn, loratadine has been shown to reduce the number of respiratory exacerbations during the treatment period in a group of children with repeated ear, nose and throat infections (5 or more), without prior asthma [43].

A metaanalysis has reviewed the efficacy of oxatomide in relation to stable asthma control in adults and children. The study concluded that there is no scientific evidence that this drug exerts a significant effect upon the control of stable asthmatic disease - though a number of studies reported benefits in terms of subjective parameters. The adverse effects were greater with oxatomide than with placebo [44].

Efficacy of antihistamines in the treatment of atopic dermatitis in children

The Alergológica 2005 epidemiological study [1] showed that 73.6% of the children diagnosed with atopic dermatitis and included in the study were prescribed antihistamine therapy - a first-generation drug being involved in 20% of the cases.

The physiopathology of atopic dermatitis is complex and involves multiple cell populations, which in turn produce a range of cytokines and chemokines that interact with each other. One feature is the presence of mast cells within the papillary and reticular dermis of the affected skin areas, where histamine appears to play a role as cofactor in itching.

Antihistamines are widely used to treat this disease, despite the fact that there are no clinical studies of sufficient methodological quality to warrant such generalized practice. A metaanalysis has reviewed the existing scientific evidence on the efficacy of antihistamines in reducing pruritus due to atopic dermatitis. The conclusion was that there is scant objective evidence of any relief of this symptom, and that antihistamine efficacy in application to atopic dermatitis remains to be demonstrated [45]. As an anecdote, this metaanalysis mentions that the sedating antihistamines have been found to be useful in some studies, thanks to their capacity to induce drowsiness or sedation. However, there is one study that has concluded that chlorpheniramine is not more effective than placebo in ameliorating the symptoms of childhood atopic dermatitis with nocturnal itching and scratch marks, and that antihistamine use does not affect the amount of topical treatment used over the short term [46].

In a clinical study published after the aforementioned metaanalysis, it was concluded that cetirizine reduces the
duration and amount of topical corticoid treatment used in children with the worst atopic dermatitis (according to the SCORAD index) [47].

**Efficacy of antihistamines in the treatment of childhood urticaria**

Acute urticaria is the most common type of urticaria in the pediatric population, and is normally caused by an immediate hypersensitivity reaction to some food, or following viral infections. Chronic urticaria is much less common in children, and an important percentage of diagnosed cases correspond to physical causes [1,48]. The Alergológica 2005 epidemiological study [1] showed 82.3% of the cases of urticaria in children under 14 years of age included in the study were of an acute nature, while the remaining 17.7% of cases were diagnosed as chronic presentations [1].

In adults, the H1 antihistamines have demonstrated their efficacy in alleviating urticaria symptoms, though to date no studies of the required methodological quality have been conducted in children with urticaria of any origin.

In another study carried out in children presenting atopic dermatitis, and involving cetirizine administered with the purpose of preventing the development of asthma, a prophylactic effect was demonstrated in relation to acute urticaria, since during the 18 months of active treatment the number of acute urticaria episodes was significantly lower than in the placebo series - an effect that did not persist during 18 months of follow-up without active treatment [49].

**Efficacy of antihistamines in the treatment of anaphylaxis in children**

Few data have been published on the role of antihistamines in the treatment of anaphylaxis in children.

A study has assessed the role of promethazine in the prevention of anaphylaxis following the bite of a type of snake found in tropical South America (mapanare) - no significant performance in favor of the active treatment group versus placebo being found [50].

In a review of 22 cases of idiopathic anaphylaxis in children, treatment including hydroxyzine and in some cases ketotifen proved successful in improving patient response to corticoids. Intramuscular adrenalin was always on hand for immediate treatment, and the antihistamine was used as an adjuvant for symptoms control [51].

**Efficacy of antihistamines in the treatment of respiratory tract infections in children**

Formulations containing antihistamines only, or in combination with other drugs (antitussive agents, systemic decongesting drugs, etc.), are widely used for symptoms control and the treatment of respiratory tract infections in children.

A metaanalysis has reviewed the usefulness of antihistamine treatment in application to the common cold, concluding that these drugs administered as monotherapy in adults and children afford no clinical relief of nasal congestion, rhinorrhea or sneezing, and do not subjectively improve the common cold. Moreover, the first-generation antihistamines induced more side effects than placebo, particularly increased sedation in the patients with a common cold. The combinations of antihistamines with decongesting agents are not effective in small children. In older children and in adults, most studies report a beneficial effect in terms of general recovery, as well as in the nasal symptoms, when these combinations are used. However, the metaanalysis also concludes that the clinical relevance of these effects is not clear (Figure 4) [52].

In another study designed to determine whether continued treatment with a non-sedating antihistamine (loratadine) is able to prevent upper airways infections, the only conclusion was that children administered the drug suffered fewer respiratory exacerbations during the active treatment phase than the placebo group - though this protective effect disappeared on suspending the treatment [43]. This study concluded that the upper airways infections rate in children at risk of suffering such infections decreases considerably with age, and is not significantly influenced by treatment with loratadine.

**Efficacy of antihistamines in the treatment of otitis media in children**

Otitis media is the most common cause of childhood hearing loss, and is one of the most common reasons for visiting the pediatrician [53]. Elevations in histamine concentration in the middle ear effusions of patients with otitis media have been demonstrated [54], along with elevations in other allergic inflammation mediators. The use of antihistamines in application to this pathology therefore could be justified.

A metaanalysis has reviewed the efficacy of antihistamines either alone or in combination with decongesting agents, in the treatment of otitis media with effusion (seromucosal otitis). No statistically or clinically significant benefit was observed in relation to any of the interventions or results considered. Nevertheless, the treated subjects suffered an 11% greater incidence of side effects than the non-treated patients. The calculated number-needed-to-treat (NNT) to cause an adverse effect was found to be 9. The authors of the study therefore recommended that such therapy should be avoided. As regards the research implications, this systematic review concluded that antihistamines may be useful specifically for seromucosal otitis in allergic patients [55].

Another metaanalysis has reviewed the effect of antihistamines (and of nasal decongestants) in application to acute otitis media in children. The study concluded that only the group administered active treatment with the combination of both types of drug showed clinically significant improvement - though the benefit in any case was small, and the study design may have biased the results.
which tends to accompany rhinitis - since many studies designed to assess antihistamine efficacy in rhinitis included some variable for assessing the effect of treatment upon conjunctivitis.

Topical ketotifen applied to the eye is able to significantly reduce ocular itching after conjunctival provocation with the causal allergen [59].

Emedastine and levocabastine in ophthalmological solution have been shown to alleviate the symptoms of allergic conjunctivitis in children - symptoms reduction being significantly greater with emedastine than with levocabastine [60].

A study made with azelastine in eyedrops showed this topical solution to significantly reduce the symptoms of nonspecific conjunctival hyper-responsiveness in children with allergy to dust mites who presented this syndrome [61].

Likewise, azelastine was seen in another study to significantly reduce the symptoms scores in small children with seasonal allergic conjunctivitis, compared with placebo [62].

A study has also been published comparing the efficacy of levocabastine versus sodium cromoglycate (both as topical ophthalmological formulation) for the control of symptoms of seasonal allergic conjunctivitis when used upon demand versus continuous nasal spray treatment. Both treatment modalities were found to be equally effective, though the investigators concluded that for certain symptoms such as sneezing, lacrimation and nasal congestion, levocabastine was significantly better than sodium cromoglycate in reducing such manifestations [63].

### Other uses without indication

Studies have been published that demonstrate the efficacy of antihistamines in relation to indications not contemplated in the Summary of Product Characteristics. Examples include loratadine for the prevention of mosquito bite reactions in sensitive children [64], the itching of varicella [65], ketotifen...
in ulcerative colitis [66], cetirizine in eosinophilic cellulitis [67], as premedication in anesthesia [68-70], the treatment of nausea and vomiting caused by antineoplastic treatment in children [71], or for reinforcing chloroquine treatment in children with malaria [72].

Role of antihistamines as antiinflammatory medication in children

The efficacy of antihistamines is attributed mainly to their antagonistic effect upon the histamine receptors. We now know that these receptors exhibit constitutive spontaneous activity, and that the antihistamines act as reverse agonists upon them - inactivating the activated conformation and reducing the mentioned constitutive activity. The H1 receptor has been associated with many actions in relation to allergic inflammation, such as rhinorrhea, smooth muscle contraction, and many forms of itching (pruritus). This is mediated by the transduction of extracellular signals through G protein and intracellular second messengers (inositol triphosphate, diacylglycerol, phospholipase D and A2, and increases in intracellular calcium concentration). Recently there have also been reports of NF-κB transcription factor activation by the H1 receptors, which would explain the antiinflammatory actions of antihistamines via this route – since the mentioned transcription factor is associated with actions such as the regulation of adhesion molecules, chemotaxis, proinflammatory cytokine production, and antigen presentation [73].

A number of clinical studies in children have shown that cetirizine reduces leukotriene production in vitro [74], reduces nitric oxide (NO) production [75] and the presence of ICAM-1 at endothelial cell membrane level [76], induces a change in Th1/Th2 balance in favor of a Th1 response, with increases in IFN-gamma and IL-10 [77], and reduces cytokines and inflammatory cell infiltrates [78].

Ketotifen, in a clinical study versus montelukast, was seen to reduce plasma cytokines to a greater extent than montelukast, in children with persistent mild asthma [79].

Antihistamines have demonstrated antiinflammatory effects in clinical studies in children, both ex vivo and in vivo. The true relevance of this antiinflammatory action in relation to the clinical effect of antihistamine treatment remains to be established.

One of the most important questions in this context is the relevance of prescribing antihistamine treatment on an intermittent or continuous basis with the purpose of preventing the development of disease in asymptomatic subjects presumed to present a persistent minimal inflammatory process. A recent clinical study has explored this aspect, administering desloratadine on an intermittent basis (upon demand) or regularly in children diagnosed with allergic rhinitis secondary to pollen sensitization. The study concluded that both treatment regimens are equally effective in terms of rhinitis control, but that regular administration afforded better control of the symptoms of bronchial hyper-responsiveness, with a lesser use of bronchodilators upon demand, and with better results in the methacholine provocation tests [80].

Adverse effects and safety issues of antihistamine use in children

The different national and international drug agencies admit that there are currently many medicines authorized for use in children that have never been adequately investigated for application in such patients - though in their day they received authorization out of a lack of regulation of the required specifications. In this sense, their use is still allowed because the pharmacovigilance systems have not detected any adverse effects requiring their withdrawal from the market. Many of the antihistamine indications in children have been based on the extrapolation of the effects of these drugs in adults. Worse still, calculation of the pediatric doses has been done with little or no pharmacokinetic data corresponding to the different pediatric age groups.

1. First-generation antihistamines

The first-generation antihistamines extensively cross the blood-brain barrier, and therefore exert an important effect upon the central nervous system. Few studies have explicitly investigated the effect of first-generation antihistamines upon the central nervous system in children, though some data have been obtained from comparative studies contrasting first- and second-generation antihistamines.

The first-generation antihistamines, diphenhydramine and hydroxyzine, were objectively assessed for effects upon cognitive processes - P300 potential latency - and drowsiness using a visual analog scale (VAS), in children with allergic rhinitis. The study concluded that both drugs induce objective dysfunction at central nervous system level, and drowsiness [81].

Another clinical trial evaluated the action of chlorpheniramine, terfenadine and placebo upon the central nervous system in a group of children with allergic rhinitis - concluding that neither terfenadine nor placebo induced cognitive changes, in contrast to chlorpheniramine [82].

In another study of 24 children between 7 and 14 years of age diagnosed with allergic rhinitis, it was seen that both chlorpheniramine and cetirizine induces significant cognitive alterations versus placebo, though such alterations were not correlated to subjective appraisal of dysfunction as assessed by means of a visual analog scale [83].

In addition to the effects upon the central nervous system, the first-generation antihistamines - as a result of their action upon receptors other than the histamine receptors - can cause adverse effects (as has been reported in the literature) including vision alterations, mucosal membrane dryness and other effects derived from the anticholinergic action of these drugs.

As a result of their action upon the serotoninergic receptors, some antihistamines can induce an increase in appetite and body weight gain. In the case of cyproheptadine, this particular effect has been known for a long time (initially reported in 1962), and is presently used as a therapeutic indication [84,85].

There have been reports of many rare adverse effects in children administered first-generation antihistamines, including spasms [86], seizures [87], aggressivity [88], respiratory distress [89], fixed skin rash [90], central...
anticholinergic syndrome [91,92] and toxic encephalopathy in patients with skin syndromes (atopic dermatitis, varicella) involving damage to the skin barrier, in whom first-generation antihistamines were applied topically [93]. It is important to consider the consequences of either accidental or intentional overdose of these drugs in children. As a result of their action upon different types of receptors (histaminic, serotoninergic, cholinergic, dopaminergic), the first-generation antihistamines are potentially lethal in cases of overdose, and both deaths and serious toxicity have been documented in pediatric patients [94,95].

2. Second-generation antihistamines

The second-generation antihistamines are known as non-sedating antihistamines because they do not cross the blood-brain barrier - a fact that minimizes their action upon the central nervous system.

Their few adverse effects and good tolerance have been well documented in many clinical studies, involving administration over long periods of time, and in almost all pediatric age groups [2]. Thus, cetirizine [27,96], levocetirizine [28,29], loratadine [17,30], desloratadine [97,98], ebastine [99] and fexofenadine [31] all have well documented safety over the short and middle term, and some also over the long term.

An important point arising from antihistamine action upon the central nervous system is how such actions can affect school performance. Since allergic rhinitis itself is able to affect school performance, because of the symptoms involved and the impairment of sleep quality, it is important to assess the impact of treatment and its adverse effects in relation to the disease and to improvement or worsening of school performance. A clinical study comparing loratadine and diphenhydramine concluded that loratadine improved academic performance, in contrast to diphenhydramine, which worsened it [100]. Another study evaluated the impact of long-term cetirizine treatment in children with atopic dermatitis - concluding that there were no adverse effects upon learning [101].

A very important issue emerged in the nineties when cardiac adverse effects were reported (arrhythmias) in relation to second-generation antihistamine use. It has been demonstrated that such effects are not class effects but rather are related to each particular molecule [73], and there have been reports in children of syncope during or after exercise, loss of consciousness or palpitations [102] with the administration of astemizole. Both this latter drug and terfenadine have been removed from the market in the great majority of countries because of this effect, and the new antihistamines are required to pass strict safety controls in relation to potential cardiotoxicity, before being authorized for introduction on the market.

The absence of cardiotoxicity with antihistamines such as cetirizine [103], loratadine [103], fexofenadine [104] and ebastine [105] has been well established. Since they have been marketed only recently, both levocetirizine and desloratadine have been required to document the absence of such cardiotoxicity according to very strict criteria, based on the new demands of the international drug agencies, in order to be authorized for use in pediatric patients - though no published studies are available.

To date, the pharmacovigilance systems have received no reports of arrhythmias related to administration of the rest of the second-generation antihistamines at both therapeutic doses and in cases of overdose.

Conclusions

In the last two decades many clinical studies of sufficient methodological quality have been made and published - thus allowing consolidation of the indication for the application of second-generation antihistamines to allergic rhinitis in children. Although the level of scientific support of the use of antihistamines for the treatment of mild to moderate asthma, fundamentally in relation to ketotifen, is limited by the questionable quality of the studies published and analyzed in the context of metaanalyses, the use of this antihistamine nevertheless can be recommended. In dermatological alterations such as atopic dermatitis or chronic urticaria, the indication remains to be established. In some cases, and despite the widespread prescription of antihistamines, the existing scientific evidence advises against their use - as in the common cold, seromucosal otitis, or nonspecific cough.

Special caution is required when establishing indications not contained in the Summary of Product Characteristics, or which have not been investigated in the drug development phase or expressly in the postmarketing period (such as sedation, analgesia or the prevention of vomiting), since the potential adverse effects - particularly with the first-generation antihistamines - make the safety of such practices questionable to say the least.

It also must be commented that many of these first-generation antihistamines, with authorization in the Summary of Product Characteristics for pediatric use, are over-the-counter (OTC) drugs freely available in pharmacies - a fact that adds to the potential for adverse effects.

Table 2 reports the degree of recommendation and the levels of scientific evidence according to the classification of Shekelle et al. [106], based on the publications considered in this review.

Table 2. Evidence in support of antihistamine use in different pathologies

<table>
<thead>
<tr>
<th>Clinical picture</th>
<th>Degree of evidence (Level of recommendation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinoconjunctivitis</td>
<td>1b (A)</td>
</tr>
<tr>
<td>Asthma (only ketotifen)</td>
<td>1a (A)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>2b (B)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1b (A)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>3 (C)</td>
</tr>
<tr>
<td>Respiratory infections *</td>
<td>4 (D)</td>
</tr>
<tr>
<td>Otitis media *</td>
<td>4 (D)</td>
</tr>
</tbody>
</table>

* The existing evidence advises against use in these clinical conditions, due to the risk of adverse effects
In conclusion, and on the basis of the present review, it seems clear that the non-cardiotoxic second-generation antihistamines are the drugs of choice for the recommended treatment indications, for patients of all ages. In this context, the first-generation drugs should be held in reserve for infrequent situations where their adverse effects may prove desirable, or when parenteral dosing is required.

It appears necessary to continue focusing research on concrete population subgroups or specific indications (seromucosal otitis, asthma in allergic children, etc.), in order to warrant these indications and further define aspects such as the dosage and the treatment regimen best suited to each individual case.

References


II Alfonso del Cuvillo

Clínica Dr. Lobatón.
Avenida Fernández Ladreda N° 9
Cádiz 11008
Spain
E-mail: dr.cuvillo@comcadiz.es