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.

Key words: Antihistamines. Pediatrics. Children. Allergic rhinitis. Atopic dermatitis. Allergic conjunctivitis.

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 fármaco 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.

Palabras clave: Antihistamínicos. Pediatría. Niños. Rinitis alérgica. Dermatitis atópica. Conjuntivitis alérgica.

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 drugs, 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 1. Pharmacological characteristics of the first- and second-generation antihistamines most commonly used in pediatric patients.

Drug	Dose (mg or mg/kg*)	Patients (no.)	Age (years)	Cp max (ng/ml)	Tmax (h)	$T_{1/2}$ (h)	erythema/wheal (h)
First generation							
Brompheniramine	4	14	9.5 ± 0.4	7.7 ± 0.7	3.2 ±0.3	12.4 ± 1.1	0.5 to 36
Chlorpheniramine	0.12*	11	11 ± 3	13.5 ± 3.5	2.5 ± 1.5	13.1 ± 6.3	1 to 24
Diphenhydramine	1.25*	7	8.9 ± 1.7	81.8 ± 30.2	1.3 ± 0.5	5.4 ± 1.8	1 to 12
Hydroxyzine	0.7*	12	6.1 ± 4.6	47.4 ± 17.3	2.0 ± 0.9	7.1 ± 2.3	n/d
Ketotifen	1 (c/12h)	6	3 ± 1	3.25	1.33	n/d	n/d
Second generation							
Cetirizine	5	10	8 ± 0.6	427.6 ± 144.2	1.4 ± 1.1	7.1 ± 1.6	1 to 24
	10	9	8 ± 0.6	978.4 ± 340.6	0.8 ± 0.4	6.9 ± 1.6	0.5 to 24
	5	8	2.7	560 ± 200	1.44 ± 1.1	4.9 ± 0.6	n/d
	0.25	15	12.3 ± 5.5m	390 ± 135	2 ± 1.3	3.1 ± 1.8	90% at 12 h
Ebastine	5	10	7.3 ± 0.4	108.6 ± 11.8	2.8 ± 0.3	11.4 ± 0.7	0.5 to 28
	10	7.8 ± 0.4	209.6 ± 24.2	3.4 ± 0.4	10.1 ± 1.1	0.5 a 28	
Fexofenadine	30 (c/12 h)	14	9.8 ± 1.8	178 ± 22	2.4 ± 0.2	18.3 ± 1.2	1 to 24
	60 (c/12h)	14	9.8 ± 1.8	286 ± 34	2.4 ± 0.2	17.6 ± 1	1 to 24
Loratadine	10	13	10.6	4.38	1	13.79	1 to 12
	5	18	3.8 ± 1.1	7.8	1.2	n/d	n/d
Levocetirizine	0.125* (c/12h)	15	20.7 ± 3.7m	286 ± 68	1	4.1 ± 0.67	1 to 28
	0.18*	14	8.6 ± 0.4	450 ± 37	1.2 ± 0.2	5.7 ± 0.2	n/d
Desloratadine	N 183 (76.3%)	58	>6m-<1				
	1.25		1-2				

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.

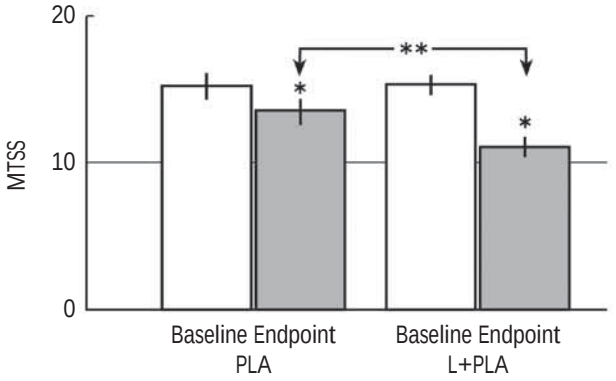

Figure 1. Taken from reference 32. In this placebo controlled and masked study, both the placebo group and the active treatment group showed significant differences in total symptoms score versus baseline - though in the active treatment series the total score was significantly more reduced than in the placebo group.

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.

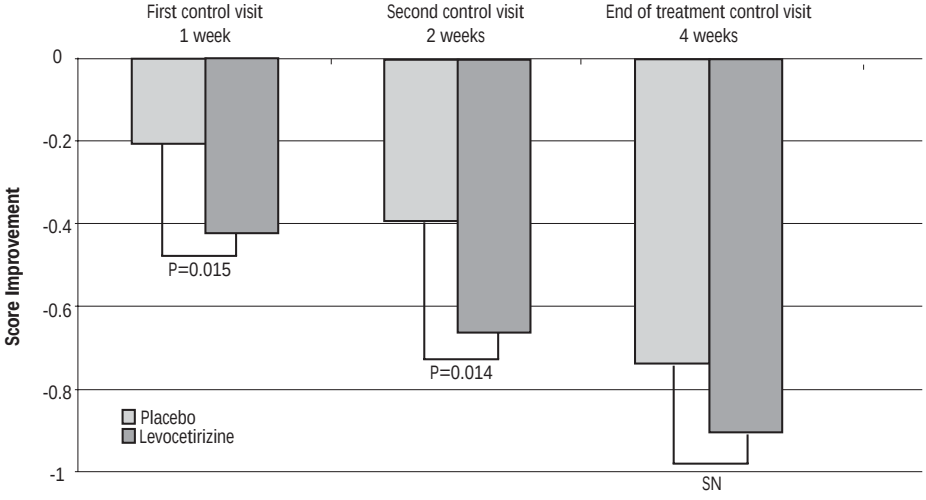

Figure 2. Taken from reference 29. Improvement in the score of the Juniper pediatric quality of life questionnaire (PRQLQ) in a series of 306 children between 6-12 years of age randomized to receive levocetirizine or placebo as treatment for allergic rhinitis during four weeks, with double-blind masking.

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].

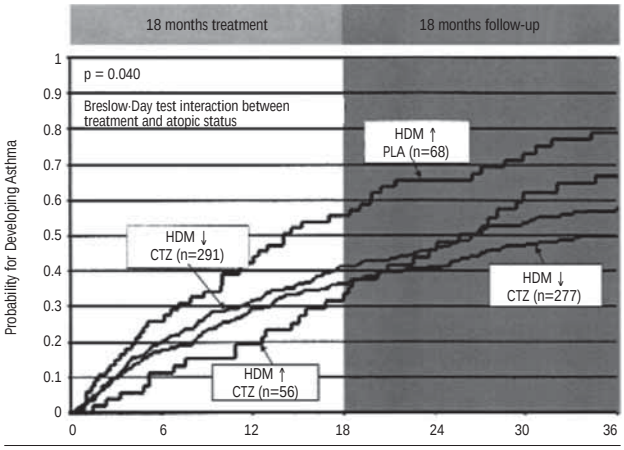

Figure 3. Taken from reference 42. Probability of developing asthma in children according to treatment with placebo or cetirizine, and according to specific IgE levels for house dust mites.

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.

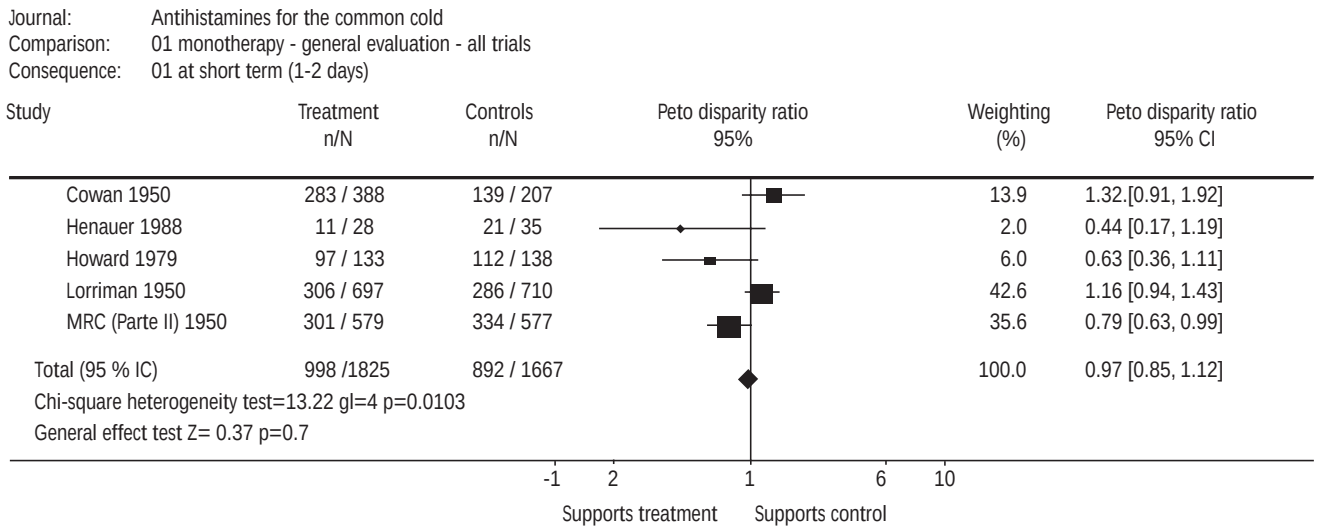

Figure 4. Taken from reference 52. Metaanalysis of the efficacy of antihistamines in alleviating the symptoms of the common cold (general evaluation), over the short term.

The observed risk of adverse events was 5- to 8-fold greater among the active treatment patients than in the placebo series, and this difference proved significant for the groups receiving treatment with decongesting agents [56].

Other uses of antihistamines in children

1. Antihistamine efficacy in application to cough

A metaanalysis reviewing antihistamine effectiveness in the treatment of prolonged nonspecific cough in children concluded that on the basis of the existing scientific evidence, empirical treatment with these drugs cannot be recommended - in contraposition to the recommendations in adults. The analysis also stressed that the systematic review posed important limitations, since only three studies with marked methodological differences could be included. It was thus concluded that if antihistamine treatment is decided, it should be discontinued if no response is elicited within two weeks [57].

Another metaanalysis evaluated the efficacy of antihistamines in acute cough in children - concluding that antihistamines in combination with decongestants (brompheniramine/phenylpropanolamine and brompheniramine/phenylephrine/propanolamine) was no superior to placebo in the two studies included, and that antihistamines alone (clemastine and chlorpheniramine) afforded no greater benefit than placebo in another study [58].

2. Antihistamine efficacy in application to allergic conjunctivitis

Although few studies unequivocally and independently document the efficacy of antihistamines in application to allergic conjunctivitis, there are sufficient to date to indicate that antihistamines are effective in treating this disorder, 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].

3. 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

Clinical picture	Degree of evidence (Level of recommendation)
Allergic rhinoconjunctivitis	1b (A)
Asthma (only ketotifen)	1a (A)
Atopic dermatitis	2b (B)
Urticaria	1b (A)
Anaphylaxis	3 (C)
Respiratory infections *	4 (D)
Otitis media *	4 (D)

* 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

1. Garde Garde J Ma, Ibáñez Sandín Ma D. Alergia en Menores de 14 años. In: Alergológica 2005. Factores epidemiológicos, clínicos y socioeconómicos de las enfermedades alérgicas en España en 2005. Madrid. Luzan 5, S.A. de Ediciones. 2006:325-387.
2. Simons FE. H1 antihistamines in children. Clin Allergy Immunol. 2002;17:437-464.
3. Simons FER, Roberts JR, Gu X, Kapur S, Simons KJ. The clinical pharmacology of brompheniramine in children. J Allergy Clin Immunol. 1999; 103:223-226.
4. Simons FER, Luciuk GH, Simons KJ. Pharmacokinetics and efficacy of chlorpheniramine in children. J Allergy Clin Immunol. 1982;69:376-381.
5. Simons KJ, Watson WTA, Martin TJ, Chen XY, Simons FER. Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults and children. J Clin Pharmacol. 1990;30:665-671.
6. Simons FER, Simons KJ, Becker AB, Haydey RP. Pharmacokinetics and antipruritic effects of hidroxyzine in children with atopic dermatitis. J Pediatr. 1984;104:123-127.
7. Schmidt-Redeman B, Brenneisen P, Schmidt-Redeman W, Gonda S. The determination of pharmacokinetic parameters of ketotifen in steady state in young children. Int J Clin Pharmacol Ther Toxicol. 1986;24:496-498.
8. Watson WTA, Simons KJ, Chen XY, Simons FER. Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. J Allergy Clin Immunol. 1989;84:457-464.
9. Desager JP, Dab I, Horsmans Y, Harvengt C. A pharmacokinetic evaluation of the second generation H1-receptor antagonist cetirizine in very young children. Clin Pharmacol Ther. 1993;53:431-435.
10. Spicak V, Dab I, Hulthoven R, Desager J-P, Klanova M, De Longueville M, Harvengt C. Pharmacokinetics and pharmocodynamics of cetirizine in infants an toddlers. Clin Pharmacol Ther. 1997;61:325-330.
11. Pitsiu M, Hussein Z, Majid O, Aaron L, de Longueville M, Stockis A. Retrospective population pharmacokinetic analysis of cetirizine in children aged 6 months to 12 years. Br J Clin Pharmacol. 2004;57:402-411.
12. Simons FE, Johnston L, Simons KJ. Clinical pharmacology of the H1-receptor antagonist cetirizine and loratadine in children. Pediatr Allergy Immunol. 2000; 11:116-119.
13. Simons FER, Watson WTA, Simons KJ. Pharmacokinetics and pharmacodynamics of ebastine in children. J Pediatr. 1993;122:641-646.
14. Simons FER, Bergman JN, Watson WTA, Simons KJ. The clinical pharmacology of fexofenadine in children. J Allergy Clin Immunol. 1996; 98:1062-1064.
15. Krishna R, Krishnawami S, Kitner B, Sankoh AJ, Jensen BK. The utility of mixed-effects covariate analysis in rapid selection of doses in pediatric subjects: a case study with fexofenadine hydrochloride. Biopharm Drug Dispos. 2004; 25:373-387.
16. Lin CC, Radwanski E, Affrime MB, Cayen MN. Pharmacokinetics of loratadine in pediatric subjects. Am J Ther. 1995;2:504-508.
17. Salmun LM, HerronJM, Banfield C, Padhi D, Lorber R, Affrime MB. The pharmacokinetics, electrocardiographic effects and tolerability of loratadine syrup in children aged 2 to 5 years. Clin Ther. 2000;22:613-621.
18. Simons FE, the ETAC study group. Population pharmacokinetics of levocetirizine in very young childrIn: the pediatricians' perspective. Pediatr Allergy Immunol. 2005;16:97-103.
19. Hussein Z, Ptisius M, Majid O, Aarons L, de Longueville M, Stockis A, ETAC Study group. Retrospective population pharmacokinetics of levocetirizine in atopic children receiving cetirizine: the ETAC study. Br J Clin Pharmacol. 2005; 59:28-37.
20. Cranwick N, Turkizova J, Fuchs M, Hulhoven R. Levocetirizine in 1-2 year old childrIn: pharmacokinetic and pharmacodynamic profile. Int J Clin Pharmacol Ther. 2005;43:172-177.
21. Simons FE, Simons KJ. Levocetirizine: pharmacokinetics and pharmacodynamics in children age 6 to 11 years. J Allergy Clin Immunol. 116: 355-361.
22. Gupta SK, Kantesaria B, Banfield C, Wang Z. Desloratadine dose selection in children aged 6 months to 2 year: comparison of population pharmacokinetics between children and adults. Br J Clin Pharmacol. 2007; Epub ahead of print.
23. Okonkwo CA, Coker HAB, Agomo PU, Ogunbanwo JA, Mafe AG, Agomo CO Afolabi BM. Effect of chlorpheniramine on the pharmacokinetics of and response to chloroquine of Nigerian children with falciparum malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1999;93: 306-311.
24. Meltzer EO. Allergic rhinitis: managing the pediatric spectrum. Allergy Asthma Proc. 2006;27:2-8.
25. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. J Allergy Clin Immunol. 1998;101:163-170.
26. Lack G. Pediatric allergic rhinitis and comorbid disorders. J Allergic Clin Immunol. 2001;108(1 suppl): S9-15.
27. Lai DS, Lue KH, Hsieh JC, Lin KL, Lee HS. The comparison of the efficacy and safety of cetirizine, oxatomide, ketotifen and a placebo for the treatment of childhood perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2002;89: 589-598.
28. De Blic J, WahnU, Billard E, Alt R, Pujazon MC. Levocetirizine in childrIn: evidenced efficacy and safety in a 6 week randomized seasonal allergic trial. Pediatr Allergy Immunol. 2005;16: 267-75.
29. Potter PC, Paediatric levocetirizine study group. Efficacy and safety of levocetirizine on symptoms and health-related quality of life in children with perennial allergic rhinitis: a double-blind, placebo controlled randomized clinical trial. Ann Allergy Asthma Immunol. 2005;95:175-180.

30. Yang YH, Lin YT, Lu MY, Tsai MJ, Chiang BL. A double-blind, placebo controlled and randomized study of loratadine (clarityne) syrup for the treatment of allergic rhinitis in children aged 3 to 12 years. Asian Pac J Allergy Immunol. 2001;19:171-175.
31. Meltzer EO, Scheimann P, Rosado Pinto JE, Bachert C, Hedlin G, Wahn U, Finn AF Jr., Ruuth E. Safety and efficacy of oral fexofenadine in children with seasonal allergic rhinitis. A pooled analysis of three studies. Pediatr Allergy Immunol. 2004;15:253-260.
32. Serra HA, Alves O, Rizzo LF, Devoto FM, Ascierto H. Loratadine-pseudoephedrine in children with allergic rhinitis, a controlled double-blind trial. Br J Clin Pharmacol. 1998;45:147-150.
33. Baki A, Orhan F. The effect of loratadine in exercise induced asthma. Arch Dis Chile. 2002;86:38-39.
34. Ciprandi G, Tosca M, Ricca V, Passalacqua G, Fregonese L, Fasce L, Canónica GW. Cetirizine treatment of allergic cough in children with pollen allergy. Allergy. 1997;52:752-754.
35. Kabra SK, Pandey RM, Singh R, Seth V. Ketotifen for asthma in children aged 5 to 15 years: a randomized placebo controlled trial. Ann Allergy Asthma Immunol. 2000; 85 (1): 46-52.
36. Schwarzer G, Bassler D, Mitra A, Ducharme FM, Foster J. Ketotifen alone or as additional medication for long term control of asthma and wheeze in children. Cochrane Database Syst Rev. 2004; CD001384.
37. Corren J, Harris AG, Aaronson D, Beaucher W, Berkowitz R, Bronsky E, Chen R, Chervinsky P, Cohen R, Fourre J, Grossman J, Meltzer E, Pedinoff A, Stricker W, Wanderer A. Efficacy and safety of loratadina plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. J Allergy Clin Immunol. 1997;100:781-788.
38. Corren J, Manning BE, Thompson SF, Hennesy S, Strom BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. J Allergy Clin Immunol. 2004;113:415-419.
39. Corren J. The connection between allergic rhinitis and bronchial asthma. Curr Opin Pulm Med. 2007;13:13-18.
40. Iikura Y, Naspitz CK, Mikawa H, Talaricoficho S, Baba M, Sole D, Nishima S. Prevention of asthma by ketotifen in infants with atopic dermatitis. Ann Allergy. 1992;68:233-236.
41. Bustos GJ, Bustos D, Bustos GJ, Romero O. Prevention of asthma with ketotifen in preasthmatic childrIn: a three year follow-up study. Clin Exp Allergy. 1995;25:568-573.
42. Warner JO: ETAC study group. Early treatment of the atopic child. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow up. J Allergy Clin Immunol. 2001;108:929-937.
43. Grimfeld A, Holgates ST, Canonica GW, Bonini S, Borres MP, Adam D, Canseco Gonzalez C, Lobaton P, Patel P, Szczeklik A, Danzig MR, Roman I, Bismut H, Czarlewski W. Prophylactic management of children at risk for recurrent upper respiratory infection: the preventia l study. Clin Exp Allergy. 2004;34:1665-1672.
44. Hayashi K, Yanagi M, Wood-Baker R, Takamatsu I, Anami K. Oxatomide for stable asthma in adults and children. Cochrane Database Syst Rev. 2003; (2): CD002179.
45. Klein PA, Clark RA. An evidence-base review of the efficacy of antihistamines in relieving pruritus in atopic dermatitis. Arch Dermatol. 1999;135:1522-1525.
46. Munday J, Bloomfield R, Goldman M, Robey H, Kitowska GJ, Gwiezdziski Z, Wankiewicz, Marks R Protas-Drozd F, Mikaszewska M. Chlorfeniramine is no more effective than placebo in relieving the symptoms of childhood atopic dermatitis with a nocturnal itching and scratching component. Dermatology. 2002;205:40-45.
47. Diepgen TL; Early treatment of the atopic child study group. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-comtrolled trial (the ETAC trial) over 18 months. Pediatr Allergy Immunol. 2002;13:278-286.
48. Mortureux P, Léauté-Labrèze C, Legrain-Lifermann V, Lamireau T, Sarlangue J, Taieb A. Acute urticaria en infancy and early childhood. Arch Dermatol. 1998;134:319-323.
49. Simons FER, on behalf of the ETAC Study group. Prevention of acute urticaria en young children with atopic dermatitis. J Allergy Clin Immunol. 2001;107:703-706.
50. Fan HW, Marcopito LF, Cardoso JL, Franca FO, Malaque CM, Ferrari RA, Theakson RD, Warrell DA. Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. BMJ. 1999;318:1451-1452.
51. Ditto AM, Krasnick J, Greenberger PA, Kelly KJ, McGrath K, Patterson R. Pediatric idiopathic anaphylaxis: experience with 22 patients. J Allergy Clin Immunol. 1997;100:320-326.
52. Sutter AI, Lemiengre M, Campbell H, Mackinnon HF. Antihistamines for the common cold. Cochrane Database Syst Rev. 2003;3:CD001267.
53. Teele DW, Klein JO, Rosner B. Middle ear disease and the practice of pediatrics: Burden during the first years of life. JAMA. 1983;249:1026-9.
54. Chonmaitree T, Patel JA, Left-Brown MA, Uchida T, Garofalo R, Owen MJ, Howie VM. Virus and bacteria enhance histamine production in middle ear fluids of children with acute otitis media. J Infect Dis. 1994;169:1265-1270.
55. Griffin GH, Flynn C, Bailey RE, Schultz JK. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. Cochrane Database Syst Rev. 2006;4:CD003423.
56. Flynn CA, Griffin GH, Schultz JK. Decongestants and antihistamines for acute otitis media in children. Cochrane Database Syst Rev. 2004;3:CD001727.
57. Chang AB, Peake J, McElrea MS. Antihistamines for prolonged non-specific cough in children. Cochrane Database Syst Rev. 2006;3:CD005604.
58. Schroeder K, Fahey T. Over the counter medications for acute cough in children and adults in ambulatory settings. Cochrane Database Syst Rev. 2004;4:CD001831.
59. Abelson MB, Ferzola NJ, McWhirter CL, Crampton HJ. Efficacy and safety of single and multiple dose ketotifen fumarate 0.025 ophtalmic solution in a pediatric population. Pediatr Allergy Immunol. 2004;6:551-557.
60. Secchi A, Ciprandi G, Leonardi A, Deschenes J, Abelson MB. Safety and efficacy comparison of emedastine 0.05% ophthalmic solution compared to levocabastine 0.05% ophthalmic suspension in pediatric subjects with allergic conjunctivitis. Emadine Study Group. Acta Ophtalmol Acand Suppl. 2000;230:42-47.
61. Ciprandi G, Catrullo A, Tosca M, Cerqueti P, Mondino C, Passalacqua G, Canónica GW. Azelastine eye drops reduce

conjunctival hyperresponsiveness to hyperosmolar glucose challenge in children with asymptomatic mite conjunctivitis. J Investig Allergol Clin Immunol. 1999; 9 1:35-38.
62. Sabbah A, Marzetto M. Azelastine eye drops in the treatment of seasonal allergic conjunctivitis or rhinoconjunctivitis in young children. Curr Med Res Opin. 1998;14: 161-170.
63. Vermeulen J, Mercer M. Comparison of the efficacy and tolerability of topical levocabastine and sodium cromoglycate in the treatment of seasonal allergic rhinoconjunctivitis in children. Pediatr Allergy Immunol. 1994;5:209-213.
64. Karppinnen A, Kautianen H, Reunala T, Petman L, Reunala T, Brummer-Korvenkontio H. Loratadine in the treatment of mosquito-bite-sensitive children. Allergy. 2000;55:668-671.
65. English W, Bauer C-P. Dimethindene maleato in the treatment of pruritus caused by varicella zopster virus infection in children. Arzneim-Forsch/Drug Res. 1997;47:1233-1235.
66. Jones NL, Roifman CM, Grifiths AM, Sherman P. Ketotifeno therapy for acute ulcerative colitis in children. A pilot study. Digestive Diseases and Sciences. 1998;43:609-615.
67. Aroni K, Aivaliotis M, Liossi A, Davaris P. Eosinophilic cellulitis in a child successfully treated with cetirizine. Acta Derm Venereol. (Stockh) 1999;79: 332.
68. Ragg P, Davidson A. Comparison of the efficacy of paracetamol versus paracetamol, codeine and promethazine (painstop) for premedication and analgesia for myringotomy in children. Anaesth Intens Care. 1997;25:29-32.
69. Downs AT, Dembo J, Ferrerri G, Lyons TD, Pelphery A. A compartive study of midazolam to meperidine/promethazine as an IM sedative technique for the pediatric dental patient. J Dent Child. 1997;64:197-200.
70. Cengiz M, Baysal Z, Ganidagli S. Oral sedation with midazolam an diphenydramine compared with midazolam alone in children undergoing resonance imaging. Paediatr Anaesth. 2006;16:621-626.
71. Köseoglu V, Kürekci AE, Sorici U, Atay AA, Ozcan O. Comparison of the efficacy and side-effects of ondansertron and metoclopramide-diphenhydramine administered to control nausea and vomiting in children treated with antineoplasic chemotherapy: a prospective randomized study. Eur J Pediatr. 1998;157:806-810.
72. Sowunmi A, Oduola AMJ, Ogundahunsi OAT, Falade CO, Gbotosho GO, Salako LA. Enhanced efficacy of chloroquine-chlorpheniramine combination in acute uncomplicated falciparum malaria in children. Trans R Soc Tropical Med Hyg. 1997;91:63-67.
73. Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. Clin Exp Allergy. 2002;32:489-498.
74. Kalayci O, Saraclar Y, Adalioglu G, Sekerel B, Tuncer A. The effect of cetirizine on sulfidoleukotriene production by blood leukocytes in children with allergic rhinitis. Allergy. 1995;50:964-969.
75. Lanz MJ, Liu AH, Buchmeier AD, Nelson HS. Nasal nitric oxide decreases in children with grass pollen allergy with oral cetirizine syrup. J Allergy Clin Immunol. 1998;101:S244.
76. Fasce L, Ciprandi G, Pronzato C, Cozzani S, Tosca MA, Grimaldi J, Canonica GW. Cetirizine reduces ICAM-1 on epithelial cells during nasal minimal persistent inflammation in asymptomatic children with mite-allergic asthma. Int Arch Allergy Immunol. 1996;109:272-276.
77. Uguz A, Sanlioglu S, Yuzbey S, Coskun M, Yegin O. The effect of cetirizine on IFN-gamma and IL-10 production in children with allergic rhinitis. Turk J Pediatr. 2005;47:111-115.
78. Ciprandi G, Tosca MA, Milanese M, Ricca V. Cetirizine reduces cytokines and inflammatory cells in children with perennial allergic rhinitis. Allerg Immunol (Paris). 2004;36:237-240.
79. Hung CH, Li Cy, Lai YS, Hsu PC, Hua YM, Yang KD. Discrepant clinical responses and blood chemokine profiles between two non-steroidal anti-inflammatory medications for children with mild persistent asthma. Pediatr Allergy Immunol. 2005;16:306-309.
80. Dizdar EA, Sekerel BE, Keskin O, Kalayci O, Adalioglu G, Dogan C, Tuncer A. The effect of regular versus on-demand desloratadine treatment in children with allergic rhinitis. Int J Pediatr Otorhinolaryngol. 2007;71:843-849.
81. Simons FE, Fraser TG, Reggin JD, Roberts JR, Simons KJ. Adverse central nervous system effects of older antihistamines in children. Pediatr Allergy Immunol. 1996;7:22-27.
82. Simons FE, Reggin JD, Roberts JR, Simons KJ. Benefits/risk ratio of the antihistamines (H1-receptor antagonist) terfenadine and chlorpheniramine in children. J Pediatr. 1994;124:979-983.
83. Ng KH, Chong D, Wong CK, Ong HT, Lee CY, Lee BW, Shek LP. Central nervous system side effects of first- and second-generation antihistamines in school children with perennial allergic rhinitis: a randomized, double-blind, placebo controlled comparative study. Pediatrics. 2004;113:116-121.
84. Lavenstein AF, Dacaney EP, Lasagna L, Vanmetre TE. Effect of cyproheptadine on asthmatic children. Study of appetite, weight gain and linear growth. JAMA. 1962;180:912-916.
85. Homnick DN, Marks JH, Hare KL, Bonnema SK. Long term trial of cyproheptadine as an appetite stimulant in cystic fibrosis. Pediatr Pulmonol. 2005;40:251-256.
86. Yasuhara A, Ochi A, Harada Y, Kobayashi Y. Infantile spasms associated with a histamine H1-antagonist. Neuropediatrics. 1998;29:320-321.
87. Yokohama H, Iinuma K, Yanai K, Watanabe, Sakurai E, Onodera K. Proconvulsant effect of ketotifeno, a histamine H1-antagonist, confirmed by the use of d-chlorfeniramine with monitoring electroencephalography. Meth Find Exp Clin Pharmacol. 1993;15:183-188.
88. Strayhorn JM Jr. Case study: Cyproheptadine and agresión in a five-year-old boy. J Am Acad Child Adolesc Psychiatr. 1998;37:668-670.
89. Lindsay CA, Williams GD, Levin DL. Fatal adult respiratory distress síndrome after diphenydramine toxicity in a child: A case report. Crit Care Med. 1995;23:771-781.
90. Cohen HA, Barzilai A, Matalon A, Harel L, Gross S. Fixed drug eruption of the penis due to hydroxycine hydrochloride. Ann Pharmacother. 1997;31:327-329.
91. Watemberg NA, Roth KS, Alehan FK, Epstein CE. Central anticholinergic syndrome on therapeutic doses of cyproheptadine. Pediatrics. 1999;103:158-160.
92. Garza MB, Osterhoudt KC, Rutstein R. Central anticholinergic Osyndrome from orphendarine in a 3-year-old. Ped Emerg Care. 02000;16:97-98.
93. OReilly JF Jr, Weisse ME. Topically induced diphenydramine Otoxicity. J Emerg Med. 1990;8:59-61.

94. 0Goetz CM, Lopez G, Dean BS, Krenzelok EP. Accidental 0childhood death from diphenhydramine overdosage. Am J 0Emerg Med. 1990;8:321-322.
95. 0Jumbelick MI, Hanzlick R, Cohle S. Alkylamine antihistamina 0toxicity and review of pediatric toxicology registry of the 0nacional Association of Medical Examiners. Am J Forensic Med 0Pathol. 1997;18:65-69.
96. 0Simons FE, Silas P, Portnoy JM, Catuogno J, Chapman D, 0Olufade AO, Pahrmd. Safety of cetirizine in infants 6 to 11 0months of age: randomized double-blind, placebo-comtrolled 0study. J Allergy Clin Immunol. 2003;111:1244-1248.
97. 0Bloom M, Staudinger H, Herron J. Safety of desloratadine 0syrup in children. Curr Med Res Opin. 2004;20:1959-1965.
98. 0Rossi GA, Tosca MA, Passalacqua G, Bianchi B, Le Garzie C, 0Canonica GW. Evidence of desloratadine syrup efficacy and 0tolerability in children with pollen-induced allergic rhinitis. 0Allergy. 2005;60:416-417.
99. 0Ostrom N, Welch M, Morris R, Rosen J, Wanderer A, Dockhorn 0R, Tinkelman D, Vandewalker M, Ziering W. Evaluation of 0ebastina, a new non-sedating antihistamine, in children 0with seasonal allergic rhinitis. J Allergy Clin Immunol. 01994;93:163.
100. 0Vuurman EFPM, van Veggel LMA, Uiterwijk MMC, Leutner D, 0O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects 0on children's learning. Ann Allergy. 1993;71:121-126.
101. 0Stevenson J, Cornah D, Evrard P, Vanderheyden V, Billard C, 0Bax M, Van Hout A, ETAC Study Group. Long-term evaluation 0of the impact of the H1-receptor antagonist cetirizine on 0the behavioural, cognitive, and psychomotor development 0of very young children with atopic dermatitis. Pediatr Res. 02002;52:251-257.
102. 0Wiley II JF, Gelber ML, Henretig FM, Wiley CC, Sandhu S, 0Loiselle j. Cardiotoxic effects of astemizol overdose in children. 0J Pediatr. 1992;120:799-802.
103. 0Delgado LF, Pferferman A, Solé D, Naspitz CK. Evaluation of 0the potential cardiotoxicity of the antihistamines terfenadine, 0astemizol, loratadina and cetirizine in atopic children. Ann 0Allergy Asthma Immunol. 1998;80:333-337.
104. 0Graft DF, Bernstein DL, Goldsobel A, Meltzer EO, Portnoy J, 0Long J. Safety of fexofenadine in children treated for seasonal 0allergic rhinitis. Ann Allergy Asthma Immunol. 2001;87:22-026.
105. 0Moss AJ, Chaikin P, Garcia JD, Guillen M, Roberts DJ, 0Morganroth J. A review of the cardiac systemic side-effects 0of antihistamines: ebastine. Clin Exp Allergy 1999;29 suppl. 03:200-205.
106. 0Shekelle PG, Wool SH, Eccles M, Grimshaw J. Clinical 0guidelines: developing guidelines. BMJ. 1999;318:593-596.

Alfonso del Cuvillo

Clínica Dr. Lobatón.
Avenida Fernández Ladreda Nº 9
Cádiz 11008
Spain
E-mail: dr.cuvillo@comcadiz.es

