

Original article

New oral H1 antihistamines in children: facts and unmet needs

Background: Second-generation antihistamines differ from first-generation ones because of their elevated specificity and affinity for peripheral H1-receptors and because of their lower penetration to the central nervous system, having fewer sedative effects as a result. Over the last few years, new compounds with different pharmacokinetic properties have been synthesized. More recent improvements of the molecules, generally in the form of active metabolites, led to the synthesis of new-generation antihistamines.

Methods: Recommendations on the minimum criteria that would have to be met for compounds to be classified as new-generation antihistamines have been recently established by a consensus statement. In the past, the pharmacokinetics and pharmacodynamics of H1 antihistamines have not been optimally investigated in the pediatric population, especially in infants and young children.

Results: The pharmacology of second-generation H1 antihistamines has been investigated relatively deeper than old antihistamines in children. In the pediatric population, clinical studies with new-generation antihistamines are still limited in number and, with rare exceptions, of brief duration. Comparative trials on the efficacy and safety between different compounds are also lacking.

Conclusions: Properly designed, long-term trials with new-generation H1 antihistamines need to be performed in single age groups, in order to better define the effects of these drugs in all pediatric population.

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Lack of evidence-based pediatric pharmacotherapy is a well-known phenomenon that has obvious and important implications for new therapies. There are many reasons which limit pharmacologic studies in the pediatric population, i.e. special ethical and practical issues in carrying out research on children. They include the different pharmacokinetics at different ages, from the neonatal period to adolescence, so a single 'paediatric' trial is never likely to be enough; and the challenging ethics of clinical trials in those too young to give consent for themselves (1).

Antihistamines are drugs widely prescribed for the treatment of allergic disorders. It is generally assumed that all approved antihistamines have been shown to be efficacious and safe, but many medications in this class, especially those introduced before the last 20 years, have not been studied appropriately (2). This is particularly true for children. This article focuses on the pharmacologic characteristics, actual research and clinical experience with antihistamines in children, with special emphasis for the new oral compounds.

Histamine and histamine receptors

Histamine, a primary amine synthesized and released predominantly by immunologic/nonimmunologic stimulation of mast cells and basophils, plays a key role in the

pathogenesis of allergic diseases, in particular rhinitis and urticaria (3). Allergen challenge studies have demonstrated that concentrations of histamine are increased in the nasal secretions of patients with allergic rhinitis, and in plasma and skin lesions of patients with urticaria (3). There is also increasing evidence that histamine influences the maturation and/or activity of several inflammatory, effector and immunologic cell types (including neutrophils, eosinophils, macrophages, monocytes, T-cells, epithelial cells, and endothelial cells), and therefore directly or indirectly elicits proinflammatory and immunomodulatory effects (4, 5).

It is now understood that histamine exerts its effects in allergic disease by interacting mainly with one of the four histamine-receptor subtypes – H1, H2, H3, and H4. These receptor subtypes belong to the superfamily of G-protein-coupled receptors and differ in their location, second messengers, and histamine-binding properties (6). H1- and H2-receptors are widely expressed in humans, in contrast to H3- and H4-receptors.

Histamine exerts its effects in allergic diseases primarily interacting with H1-receptors present in a variety of organs. Interaction of histamine with the Gq/11-coupled H1-receptor, in particular, leads to initiation of intracellular signaling pathways and activation of the transcription nuclear factor- κ B, ultimately resulting in expression of many of the classic symptoms of allergic rhinitis and of itching in urticaria (5).

In the nose, histamine stimulates the sensory nerve endings (itching and sneezing), increases vascular permeability (edema and obstruction), and induces glandular secretions (rhinorrhea). In the skin, it provokes vasodilation (erythema and edema) and stimulates sensory nerve endings (itching). In the lungs, it primarily acts on the bronchial smooth muscle (bronchoconstriction) (7).

A greater understanding of the mechanisms underlying histamine and H1-receptor activation has led to the development of several efficacious and well-tolerated H1-receptor antagonists (H1 antihistamines), which are currently considered the first-line therapy for the management of allergic rhinitis and urticaria (8, 9).

Classification of H1 antihistamines

H1 antihistamines differ significantly in terms of their chemical structure, clinical pharmacology, and toxicity potential (10). Traditionally, they have been classified into six categories: the ethanolamines, ethylenediamines, alkylamines, piperazines, piperidines, and phenothiazines (Table 1). Depending on their action on the central nervous system (CNS), they are more commonly classified as first-generation, which are sedating, and second-generation, which are relatively nonsedating. It should be emphasized that many of the second-generation H1 antihistamines are the result of modification of existing compounds, and then are chemically related to them.

In general, first-generation H1 antihistamines are rapidly absorbed and metabolized, which means they must be administered three or four times a day. Because of their particular molecular structure, they cross the

blood–brain barrier, bind easily to the cerebral H1-receptors and thereby create their principal side-effect, sedation.

Over the last two decades, second-generation H1 antihistamines were synthesized compounds with high potency, long-lasting effect, and minimal adverse effects. They are unlikely to cross the blood–brain barrier and rarely cause sedation. As a result of their high affinity for the H1-receptors and prolonged half-life, they need only be taken once or twice a day (Table 2).

In order to better improve the therapeutic index of second-generation H1 antihistamines, later refinements led to the synthesis of other compounds, many of them in the form of active metabolites. These drugs had been inappropriately defined, with no clear description of meaning, as 'third-generation antihistamines', which undoubtedly created much confusion among general practitioners and health professionals. To overcome this aspect, a Consensus Group on New Generation Antihistamines (CONGA) was established, resulting in recommendations on the minimum criteria that would have to be met for compounds to be classified as new-generation antihistamines (11).

Effects on the H1-receptor

For years it was believed that H1 antihistamines acted as competitive histamine antagonists, blocking the site where histamine binds with receptors. Recently, the H1-receptor has been shown to exist in both active and inactive isoforms that are in equilibrium on the cellular surface, and respond to the agonist (histamine) and 'inverse agonists' (antihistamines), respectively (6). It was realized that the receptors have an agonist-independent signal transduction, in other words, even in the absence of histamine they are constitutively in the 'on' position – activate. H1 antihistamines act as 'inverse agonists' that combine with and stabilize the inactive isoform of the H1-receptor, then shifting the equilibrium towards the inactive state (6).

The efficacy of H1 antihistamines for treatment of allergic diseases has been traditionally attributed to their capacity to downregulate the activity of histamine on H1-receptors located on endothelial cells, airway smooth muscle, and sensory nerve endings. Thus, H1 antihistamines are able to: (i) reduce vascular permeability, vasodilation, and glandular secretion, and to improve rhinorrhea, erythema, and cutaneous edema; (ii) promote bronchodilation; (iii) reduce sneezing and itching of nasal mucosa and skin (9).

Anti-inflammatory effects

Chronic allergic inflammation resulting from the late-phase reaction exhibits components that are similar to

Table 1. Chemical classification of H1 antihistamines

<i>Alkylamines</i>	<i>Piperazines</i>
Brompheniramine	Buclicline
Chlorpheniramine	Cyclizine
Deslorpheniramine	Meclizine
Pheniramine	Oxatomide
Dimethindene	Hydroxyzine
Triprolidine	Cetirizine
Acrivastine	Levocetirizine
<i>Ethanolamines</i>	<i>Piperidines</i>
Carbinoxamine	Azatadine
Clemastine	Cyproheptadine
Dimenhydrinate	Ketotifen
Diphenhydramine	Loratadine
Doxylamine	Desloratadine
Phenyltoloxamine	Bilastine
<i>Ethylenediamines</i>	Ebastine
Antazoline	Terfenadine
Pyrimamine	Fexofenadine
Tripelenamine	Levocabastine
<i>Phenothiazines</i>	Mizolastine
Promethazine	Rupatadine
Mequitazine	
Trimeprazine	

Table 2. Characteristics of H1 antihistamines of different generations

First-generation H1 antihistamines	Second-generation H1-antihistamines
Usually administered in three to four daily doses	Usually administered once or twice a day
Cross the blood–brain barrier (lipophilicity, low molecular weight, lack of recognition by the P-glycoprotein efflux pump)	Do not cross the blood–brain barrier (lipophobicity, high molecular weight, recognition by the P-glycoprotein efflux pump)
Potentially cause side-effects (sedation/hyperactivity/insomnia/convulsions)	Do not cause relevant side-effects (sedation/fatigue/hyperactivity/convulsions)
No randomized, double-blind, placebo-controlled trials in children	Some randomized, double-blind, placebo-controlled studies in children
Case reports of toxicity are published regularly	No reports of serious toxicity
Lethal dose identified for infants/young children	Do not cause fatality in overdose

other forms of inflammation, including chemotaxis of inflammatory cells followed by activation and proliferation, with subsequent production and release of many chemical mediators. Among cells involved in allergic inflammation are: antigen-presenting cells (e.g., macrophages), mast cells, basophils, T lymphocytes, epithelial/endothelial cells, and eosinophils – major effectors of chronic inflammation. Cytokines, chemokines, inflammatory mediators, and adhesion molecules also contribute to this process which ultimately leads to dysfunction of the affected organ (12).

In addition to their effects on H1-receptors, many H1 antihistamines, at appropriate doses, also manifest some antiinflammatory and antiallergic activities. This property generally reflects the capacity of these drugs to affect mast cell and basophil activity, thus inhibiting the release of preformed mediators such as histamine, tryptase, leukotrienes, and others, but other antiallergic mechanisms may be activated. Several second-generation H1 antihistamines have demonstrated antiallergic properties, irrespective of their interaction with the H1-receptor. Such compounds are capable of inhibiting the influx of eosinophils to the site of allergen challenge in sensitized individuals. They can also alter adhesion molecules expression on epithelium and eosinophils, and reduce *in vitro* survival of eosinophils. Finally, some second-generation H1 antihistamines are capable, *in vitro* and *in vivo*, of altering the production of inflammatory cytokines [e.g. tumor necrosis factor (TNF)- α , interleukin (IL)-1 β and IL-6] and the Th1/Th2 balance regulation cytokines (e.g. IL-4 and IL-13) (12–18).

Pharmacokinetics and pharmacodynamics

The pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics of H1 antihistamines have not been optimally investigated in the pediatric population, especially in infants and young children. Indeed, pharmacokinetic and pharmacodynamic studies are inherently invasive and proper compliance during the experimental models is difficult to obtain in children.

In the absence of pharmacologic data with many H1 antihistamines, drug doses and dose intervals in childhood have to be extrapolated from those recommended

for adults using age de-escalation paradigms. The dose selected may therefore not be optimal, either for efficacy or safety in children. Development of organ function (i.e. gastric pH, gastric emptying time, intestinal motility, enzyme maturation, and renal function) is indeed ongoing throughout infancy and childhood, although many of the maturational changes affecting pharmacokinetic disposition of drugs are complete by around 1 year of age (19). Over the years, some progresses have been made and the pharmacology of second-generation H1 antihistamines has been investigated relatively deeper than old antihistamines (20).

New-generation H1 antihistamines

Desloratadine (DSL), fexofenadine (FXF), and levocetirizine (LCT) are considered new-generation antihistamines. Specific development objectives were pursued during the synthesis process by their precursors: i.e. DSL *vs* loratadine, improved pharmacokinetics and reduced drug–drug interactions; FXF *vs* terfenadine, improved safety and elimination of cardiotoxicity; LCT *vs* cetirizine, improved receptor affinity and selectivity. Other H1 antihistamines (i.e., bilastine, rupatadine) have been developed more recently, but the clinical experience in childhood is still missing.

Desloratadine

DSL is an active metabolite of loratadine which has high affinity for binding with H1-receptors. Despite this, it also interacts with the five subtypes of muscarinic receptors, thus suggesting that it has less selectivity for the H1-receptor than other drugs of the same generation (21). DSL is rapidly absorbed and is metabolized on its first passage through the liver via the P450 cytochrome (22). Although this would imply a potential for interaction with other drugs that are metabolized via the same route (i.e., erythromycin and ketoconazole), there is no direct evidence that this does actually take place (23, 24).

In the pediatric population, pharmacokinetic studies have been performed in infancy, as well as in pre-school and school-age children. The 1.25- and 2.5-mg doses of DSL in 2 to 5-year- and in 6- to 11-year-old children, respectively, produced pharmacokinetic values similar to

Table 3. Age-related differences of pharmacokinetic parameters of the new-generation antihistamines

	Adults	Children	Infants
Desloratadine			
$T_{\max}$ (h)	3.2	3.1–3.6	3.1–3.2
T (h)	12.2	16.4–19.4	12.4–14.6
AUC (ng/h/ml)	43.2	42.0–48.6	34.4–38.7
Fexofenadine			
$T_{\max}$ (h)	2.6	2.4	–
T (h)	14.4	18.3	–
Clearance rate (ml/min/kg)	15.3	14.4	–
Levocetirizine			
$T_{\max}$ (h)	1.2	1.2	1.0
T (h)	7.8	5.7	4.1
Clearance rate (ml/min/kg)	0.6	0.8	1.1

$T_{\max}$, time to maximum plasma concentration; T , half-life; AUC: area under the plasma concentration–time curve.

those previously observed in adults receiving a standard 5-mg dose (Table 3) (25). When children aged 6 months to 2 years were evaluated in a single-dose, open-label, pharmacokinetic study, doses of DSL of 1 mg for ≥ 6 months to 1 year, and 1.25 mg for ≥ 1 year- to ≤ 2 year-old infants resulted appropriate (26). These results support that a single daily dose of DSL can be taken in childhood.

Pharmacodynamic studies with DSL have been conducted exclusively in adults and adolescents. Using the histamine-induced skin wheal-and-flare model, DSL of 5 mg suppressed flares significantly more than placebo from 6 to 10 h and at 12 and 24 h; but, it suppressed wheals significantly only at 10 h (27). Pharmacodynamic studies with DSL using the nasal model have not been performed in children. However, a significant improvement in nasal flow and symptom score, when compared with placebo, was found in adults with allergic rhinitis subjected to nasal challenge (28, 29).

Fexofenadine

FXF, the pharmacologically active metabolite of terfenadine, exhibits high affinity and selectivity for peripheral H1-receptors. The drug is rapidly absorbed and minimally metabolized (30).

In the pediatric population, the pharmacokinetics of FXF has been evaluated in school-age children and adolescents. In such patients, pharmacokinetic parameters are similar to those reported in adults and would therefore suggest using a single daily dose (Table 3) (31).

Pharmacodynamic studies with FXF in the pediatric population have been conducted using the histamine-induced skin wheal-and-flare model. In school-age children, FXF of 30 mg did not suppress the wheal or flares significantly, achieving 40–54% wheal suppression from 2 to 7 h, and 45–68% flare suppression from 2 to 7 h, when

compared with predose baseline (32). The results of this study suggest that the daily dose of FXF in children should be higher than 30 mg, and be administered twice daily (32). In adolescents, FXF of 180 mg suppressed skin flares and wheals significantly more than placebo at all time points from 2 to 24 h and from 2 to 12 h post-treatment, respectively (27). Pharmacodynamic studies with FXF using the nasal model have not been performed in children. However, in adults with allergic rhinitis subjected to nasal challenge, FXF promoted significant improvement in nasal flow and symptom score, when compared with placebo (29).

Levocetirizine

LCT is the active *R*-enantiomer of the racemate cetirizine. It has high selectivity and affinity for H1-receptors, at which it has twice the binding affinity of cetirizine. LCT has conformation stability and is not converted to dextrocetirizine, the *S*-enantiomer, which has 30-fold less binding affinity than cetirizine at the H1-receptor. It is rapidly and extensively absorbed, and minimally metabolized. As a consequence of its pharmacokinetic characteristics, LCT appears to have a low potential for drug interactions (33).

In childhood, pharmacokinetics of LCT has been evaluated either in school-age or in very young children. Pharmacokinetic parameters in school-age children differ slightly from those reported in adults (34), but there are substantial differences with those reported in very young children (Table 3) (35, 36). The results of these studies indicate that dosing every 24 h would be expected to be effective in adults and children. In very young children, however, higher LCT doses may be needed on milligram per kilogram basis and twice daily doses may be required (34).

Pharmacodynamic studies with LCT in the pediatric population have been conducted using the skin model. LCT showed a potent and long-lasting (up to 28 h) suppressive effect on histamine-induced wheal and flare in school-age children. Mean maximum inhibition of wheals and flares occurred from 2 to 10 h and from 2 to 24 h, respectively (34). Histamine-induced cutaneous responses were also substantially inhibited in young children (aged 1–2 years) who received oral LCT at 0.125 mg/kg twice daily for 90 days (35). Pharmacodynamic studies with LCT using the nasal model have not been performed in children. In adults with allergic rhinitis subjected to nasal challenge, LCT promoted significant improvement in nasal flow and symptom score, when compared with a placebo (28, 29).

A novel pharmacologic approach

For most of the second-generation H1 antihistamines, despite faster clearances rates and shorter terminal

elimination half-life values reported in the pediatric population, the dose interval recommended for children is identical to the dose interval recommended for adults. These recommendations are based on traditional pharmacodynamic studies involving measurement of H1 antihistamine-induced suppression of the histamine-induced wheal and flare response overtime.

A novel approach is to calculate H1 antihistamine occupancies at H1-receptor sites by using receptor binding constants and unbound (free) H1 antihistamine plasma concentrations, and to correlate this value to the pharmacodynamic response. This approach was used to predict the onset and duration of suppression of the histamine-induced wheal and flare response after the administration of a 5 mg LCT dose in children (37, 38). The results corroborated the hypothesis that the kinetics of receptor occupancy are a better representative of the time course of pharmacodynamics than are the plasma pharmacokinetics. In such case, the H1-receptor occupancy data provide additional pharmacodynamic support for the appropriateness of once-daily LCT dosing in school-age children as is recommended for adults, despite faster clearance and shorter terminal elimination half-life values in the pediatric age group.

This novel approach may represent a useful tool for a more accurate evaluation of the dosing characteristics of H1 antihistamines at different ages. Studies addressed to such direction are strongly awaited for the new molecules.

Adverse effects

Central nervous system

H1-receptors can be found widely distributed throughout the CNS and, although their physiological role in these locations is not yet fully understood. H1 antihistamines can cause several effects within the CNS, namely: (i) sedation, varying from mild somnolence to deep sleep; (ii) depression, identified by symptoms such as coordination disturbance, dizziness, lassitude, and lack of concentration; and occasionally (iii) agitation (8).

For an H1 antihistamine, an important determinant of the occurrence of CNS side-effects is the greater or lesser capacity a compound has to cross the blood-brain barrier. The ability of a H1 antihistamine to penetrate the blood-brain barrier is mainly related to: (i) its chemical characteristics, such as lipophilicity and molecular weight; (ii) the existence of an active transport mechanism; (iii) the capacity of recognition by the P-glycoprotein efflux pump, which is expressed on the luminal surfaces of nonfenestrated endothelial cells in the vasculature of the CNS; and (iv) the degree of affinity for the H1-receptors in the CNS (8).

First-generation H1 antihistamines have high penetration to the CNS, owing to their high lipophilicity, low molecular weight, low recognition by the P-glycoprotein efflux pump, and a high degree of affinity for cerebral

H1-receptors. Therefore, sedation occurs with frequency, even at therapeutic doses. In contrast, second-generation H1 antihistamines penetrate the CNS poorly, owing to their greater molecular weight, lipophobicity, high recognition by the P-glycoprotein efflux pump, and low affinity for cerebral H1-receptors. Therefore, the majority of compounds in this generation, at therapeutic doses, are apparently devoid of significant side-effects on the CNS (8, 39).

Heart

Cardiotoxic effects are apparently dose-dependent, which is an extremely important fact with relation to drugs metabolized by the P450 cytochrome, as concurrent administration of compounds that compete for the same enzyme (macrolides, azolic antifungals) may reduce the rate at which the H1 antihistamine is metabolized, increasing its concentration in the plasma (8).

First-generation H1 antihistamines have antimuscarinic and α -adrenergic blockage activity and may cause dose-related prolongation of the QT interval. Adverse cardiac effects (torsades de pointes, arrhythmia, prolongation of the QT_c interval) were also reported with two second-generation H1 antihistamines, astemizole and terfenadine, when these compounds were administered at doses higher than those recommended, or in association with drugs that use the same hepatic metabolism route (8, 40). These effects are the result of a direct block to a specific class of potassium channels which control the cardiac repolarization phase, and are not related to the blockade of the H1-receptor. These drugs are not longer approved.

Other

The majority of first-generation H1 antihistamines exhibit pharmacological effects that are not related to their binding with H1-receptors. The principal of these is the anticholinergic effect, resulting from their capacity to bind to muscarinic receptors, causing dry mouth, tachycardia and urinary retention. These effects have not been reported with second-generation H1 antihistamines (8).

Safety

DSL, FXF, and LCT are minimally metabolized and so are safer than previous H1 antihistamines.

Desloratadine

DSL was shown to be sufficiently safe in childhood. No severe or serious adverse events occurred, no clinically relevant changes were noted in clinical laboratory tests values, and no significant electrocardiogram changes were found with respect to placebo, when the drug was administered for 2 weeks in children aged 2–5 years and

6–11 years at dosages of 1.25 and 2.5 mg daily, respectively (41). No clinically significant differences in vital signs, clinical laboratory tests results, or electrocardiograms, including QT_c intervals, were observed in a 4-week, multicenter, placebo-controlled study on adolescents and adults with allergic rhinitis treated with 5 mg of DSL daily (42). There are no long-term safety studies conducted with DSL.

Fexofenadine

Evidence indicates that FXF is safe and well-tolerated. Because of the cardiac side effects of its precursor, terfenadine, no other H1 antihistamine has been studied as much as FXF to investigate potential cardiotoxic effects. Its cardiovascular safety has been convincingly demonstrated at many different dosages, administered at differing intervals, in isolation or in association with other potentially cardiotoxic drugs (43).

A pooled analysis of three 2-week studies conducted in school-age children with FXF at different dosages (15, 30 and 60 mg twice daily) showed that treatment-related adverse events were similar across treatment groups and not different from placebo, with no sedative effects (44). Similar results on the safety and tolerability were obtained when twice-daily 30 mg of FXF was administered in children aged 2–5 years with allergic rhinitis, in a multicenter, placebo-controlled study (45). Long-term safety studies conducted with FXF are lacking.

Levocetirizine

LCT is a safe and well-tolerated compound. It does not interact significantly with any of the muscarinic receptor subtypes and does not therefore manifest marked anticholinergic effects. In two 4-week, large studies in 6–12-year-old children with allergic rhinitis, LCT of 5 mg daily showed a minimum incidence of adverse effects which were comparable with placebo (46, 47).

In the randomized, double-blind, Early Prevention of Asthma in the Atopic Child (EPAAC™) study, LCT of 0.125 mg/kg or placebo was administered twice daily for 18 months to a large population of infants (48). There were no significant differences between the treatment groups either in adverse events, or in height, mass, attainment of developmental milestones, and haematology and biochemistry tests. Together with the ETAC study (49), EPAAC is the longest prospective, randomized, double-blind, placebo-controlled investigations of the safety of any H1 antihistamine ever conducted in any age group.

Clinical use

In adults, the use of new-generation H1 antihistamines in allergic disorders is supported by a number of adequately

powered, randomized, double-blind, placebo-controlled trials. In children, clinical studies with these drugs are limited in number and, with rare exceptions, of brief duration. Furthermore, trials comparing different compounds are lacking, thus allowing not exploring the possibility of different therapeutic effects in specific allergic disorders. As far as quality of life is concerned, the experience in children is quite limited. This lack is surprising, as rhinitis is one of the most common pediatric diseases and its prevalence is increasing (50).

Allergic rhinoconjunctivitis

In patients with allergic rhinitis, H1 antihistamines improve nasal itching, sneezing and rhinorrhea. However, they are not so useful for controlling nasal obstruction. They also exert their effect on ocular symptoms, which are frequently associated with allergic rhinitis (5).

In adults, various H1 antihistamines have a similar efficacy for the overall relief of nasal or ocular symptoms reported by patients, differences reported for clinical benefit being small and inconsistent (51). In children, properly controlled studies with new-generation H1 antihistamines are few.

Double-blind, placebo-controlled trials in children over 12 years indicate that DSL at 5 mg daily is effective for the treatment of seasonal (52) and perennial (42, 53) allergic rhinitis, improving all nasal symptoms including obstruction (52, 53), associated non-nasal symptoms (53), and quality of life (52).

In children aged 6–11 years with seasonal allergic rhinitis, FXF at 30 mg twice daily was significantly superior to placebo in reducing the total symptom score and all individual nasal symptoms, including congestion (44). In double-blind, placebo-controlled, multicenter trials either on school-age children affected by seasonal (46) or perennial (47) allergic rhinitis, or adolescents with perennial allergic rhinitis (54), LCT at 5 mg daily was highly effective in improving all nasal symptoms including obstruction and providing greater health-related quality of life than placebo.

There is some evidence that continual use of H1 antihistamines offers greater advantage and is more effective in controlling symptoms of allergic rhinitis than an on-demand regimen (5). However, a recent study demonstrated that on-demand use of DSL during the pollen season is clinically as effective as regular treatment on nasal symptoms, nasal flow rates, and inflammatory markers (55). On the other hand, regular, long-term treatment may provide better control of airway symptoms and improved quality of life (56).

Urticaria

In adults, H1 antihistamine reduces the number, size, and duration of wheals and decreases itching, either in acute or in chronic urticaria. Surprisingly, despite the large use

of H1 antihistamines in general practice, the experience in children with urticaria is anecdotal. This finding should not be overlooked, in the light of the pathophysiologic and immunological differences of urticaria in adults and children.

To our knowledge, only one study has formally evaluated the effect of new-generation antihistamines on urticaria in a pediatric population. In the EPAAC study, LCT at 0.125 mg twice daily for 18 months in high-risk infants with atopic dermatitis, resulted significantly more effective than placebo in reducing the number of subjects who experienced acute episodes of urticaria (27.5% vs 41.6%), the mean number of episodes (0.71 vs 1.71 days), and the number of days with urticaria (4.43 vs 5.36) (57). The results of this study have substantially confirmed those obtained in a long-term study with cetirizine in a similar population (58).

Atopic dermatitis

Pruritus is the most common and least tolerated symptoms of atopic dermatitis, and even partial reduction of pruritus can result in significant improvement in quality of life for patients. However, histamine is only one of the many mediators that produce pruritus and the effect of H1 antihistamines in atopic dermatitis has been repeatedly questioned. Indeed, evidence-based studies of the effectiveness of H1 antihistamines in the management of atopic dermatitis are conflicting. First-generation H1 antihistamines have traditionally been prescribed for the treatment of pruritus for their soporific effects when given at bed time. On the other hand, second-generation antihistamines have been found to be ineffective in treating pruritus associated with atopic dermatitis (59). In the ETAC study, cetirizine for 18 months did not show a statistical difference with respect to placebo in reducing the severity of symptoms related to atopic dermatitis, as measured by SCORAD (60). A study with a similar design using LCT (EPAAC study) has been recently concluded. The results are strongly awaited by the scientific community.

Asthma

Current evidence does not support the use of H1 antihistamines in asthma. However, in patients with allergic inflammation through the upper and lower airways which result in concurrent symptoms of allergic rhinitis and asthma, the use of H1 antihistamines is reported to induce a significant decrease in the symptoms of both rhinitis and asthma, as well as decrease in the use of bronchodilators and improvement of lung function (2, 61).

The possibility of preventing the onset of asthma with H1 antihistamines in high-risk infants with atopic dermatitis has been evaluated in two long-term, double-blind, multicenter studies. While cetirizine administered regularly for 18 months was effective in delaying the

onset of asthma with respect to placebo only in a subpopulation of infants sensitized to house dust mite and/or grass pollen (49), the results have not been confirmed in a similar study conducted with LCT (J. Warner, personal communication).

Other

H1 antihistamines are often used, along or with H2 antihistamines in relieving flushing, hitching, urticaria, and rhinorrhea, which are common during anaphylaxis episodes. A recent review was unable to find good quality studies with antihistamines in the treatment of anaphylaxis. Randomized, controlled studies are needed, although these are likely to prove challenging to design and execute, especially in children (62).

Dosage and administration

In Europe, DSL is approved for the treatment of allergic rhinitis and chronic urticaria in adults, in adolescents aged ≥ 12 years, and in children aged 2–11 years. DSL is available as a standard film-coated tablet or rapidly disintegrated tablet, which is placed on the tongue immediately after opening the tablet packaging and readily disintegrates, administered with or without water. A syrup formulation of DSL (0.5 mg/ml) is also available in Europe. DSL can be administered without regard to the intake of food or grapefruit juice, and does not potentiate the effects of alcohol. Dosage adjustment is not required in patients who are slow metabolizers of DSL. As DSL is excreted in breast milk, caution is advised in the use of the drug in nursing mothers. The recommended dosage is 5 mg once daily in adults and adolescents ≥ 12 years, 2.5 mg once daily in children aged 6–11 years, and 1.25 mg once daily in children aged 2–5 years (63).

In Europe, FFX is approved for the treatment of allergic rhinitis and urticaria. FFX is available in tablet formulation and oral suspension (6 mg/ml). The recommended dosage is 120 mg once daily for adults and adolescents ≥ 12 years, and 30 mg twice daily for children aged 6–11 years. The drug should be administered before meals; fruit juices may reduce the bioavailability of FFX, therefore it is recommended that tablets be taken with water. It is not known if the drug is excreted in human milk (64).

LCT is approved in Europe for the symptomatic treatment of allergic rhinitis and urticaria, either in patients aged ≥ 2 years (oral drop formulation) or ≥ 6 years (tablet formulation). In addition, a solution formulation of LCT (0.5 mg/ml) for use in patients ≥ 2 years has been recently approved by regulatory authorities and marketed in some European countries. The recommended dosage is 5 mg once daily in patients aged ≥ 6 years and 1.25 mg twice daily in children aged 2–6 years (65).

What are the unmet needs?

Although H1 antihistamines are useful for the treatment of allergic disorders, the many different compounds might be not equally effective for the control of symptoms of the skin, nose, and lungs, as a consequence of their pharmacokinetic, pharmacodynamic, antiallergic, and anti-inflammatory properties. Furthermore, not all patients respond in the same manner to all H1 antihistamines, and those who do not benefit from one compound may respond satisfactorily to another.

Many H1 antihistamines have not been optimally investigated in children. Furthermore, there are not head-to-head comparison studies between different new oral H1 antihistamines. This should represent a warning for pediatricians and general physicians who are called to make a rational selection from among the large number of these drugs available on the market. Various H1 antihistamines have a similar efficacy for the relief of

symptoms of rhinoconjunctivitis or urticaria. However, the experience in randomized, controlled studies conducted for long periods and in young children is limited to cetirizine and levocetirizine. For such reasons, choosing a specific drug for a child with an allergic condition should be based primarily on consideration of safety and the clinical experience that has been gained with different compounds in specific age groups, especially if long-term treatment is expected.

Cloning the genes that code for the H1-receptor has opened up a new area in histamine research and has increased the chances that new H1 antihistamines with greater potency, safety, and selectivity will be developed in the near future. While we are waiting for these results, additional long-term efficacy and safety studies with new-generation antihistamines are needed in children, in order to continue to improve the evidence-based use of this medication class in allergic disorders.

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