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Safety and Tolerability of Treatments for Allergic Rhinitis in Children

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Abstract

Allergic rhinitis is a common condition in adults and children and can have a large impact on patients' health and quality of life. The aim of current allergic rhinitis therapies is to treat the subjective symptoms and to improve objective measures of the disease. Of the available treatment options for paediatric allergic rhinitis, the newer oral antihistamines and intranasal corticosteroids are first-line treatments.

First-generation antihistamines are associated with unwanted adverse effects such as cardiotoxicity, sedation and impairment of psychomotor function. Despite results from studies using first-generation antihistamines demonstrating impairment of cognitive and academic function in children, many of these agents are still commonly given to patients. The newer antihistamines, developed with the aim of being more specific for the histamine H_1 receptor and of overcoming these adverse effects, are the medication of choice in patients with mild intermittent allergic rhinitis. For children <12 years of age, three newer oral antihistamines are currently available: cetirizine, loratadine and fexofenadine. A lack of adverse

effects with these antihistamines has been demonstrated in children using EEG and psychomotor performance tests, and in clinical studies. However, issues of receptor selectivity and the potential for CNS adverse effects still remain, and further studies are warranted.

Intranasal corticosteroids are the most effective anti-inflammatory agents used for the treatment of paediatric allergic rhinitis; however, the safety of these compounds remains controversial. The safety implications associated with corticosteroids are long-term, dose-related systemic effects, such as suppression of adrenocortical function, growth and bone metabolism, and the extent of these effects is influenced by a number of factors including corticosteroid type, pharmacokinetic profile, mode of delivery and delivery device. Topical corticosteroids were introduced to reduce the systemic effects seen with the long-term use of oral agents. The intranasal corticosteroids currently available for the treatment of paediatric allergic rhinitis – beclometasone, budesonide, flunisolide, fluticasone propionate, mometasone and triamcinolone – have short half-lives and rapid first-pass hepatic metabolism; however, their pharmacokinetics vary in terms of systemic absorption, potency, binding affinity, lipophilicity, volume of distribution, and half-life. A number of studies – utilising hypothalamic-pituitary--adrenal axis function tests such as plasma cortisol levels, 24-hour urinary-free cortisol tests; stimulation tests with corticotropin (adrenocorticotropic hormone), lypressin, and corticotropin-releasing hormone; and growth assessment studies using knemometry and stadiometry – have indicated that these intranasal corticosteroids are well-tolerated in paediatric patients and do not significantly affect growth.

The wealth of clinical data and the recommendations from evidence-based guidelines suggest that both antihistamines and intranasal corticosteroids have good safety profiles in children. Nevertheless, growth should be regularly monitored in children receiving intranasal corticosteroids. Other treatments such as immunotherapy, local chromones and decongestants can also be beneficial in managing paediatric allergic rhinitis, and therapies should be considered on an individual basis.

Allergic rhinitis is an extremely common condition, the global prevalence of which varies widely;[1] a general estimate has been set at 10–25%,[2] and this figure appears to be rising. In children, allergic rhinitis is the most common chronic condition worldwide and is thought to affect up to 40% of all children and adolescents.[1,3,4]

Allergic rhinitis often remains undiagnosed in young children due to an inability to recognise symptoms when the child is unable to indicate how they feel, or because symptoms may be diagnosed as other diseases, such as respiratory infections. The risk factors for allergic rhinitis include serum IgE levels >100 IU/mL before 6 years of age, a family history of atopy, higher socioeconomic class, exposure to indoor allergens and a positive skin test for specific IgE antibodies.[5]

Allergic rhinitis can have a large impact on children's health and quality of life, causing absenteeism, reduced learning ability, depression, anxiety and family dysfunction.[6,7] For example, in the US, children with allergic rhinitis miss an estimated 2 million days of school per year.[4] In addition, more serious complications may occur if the condition is left untreated, including asthma, sinusitis, nasal polyposis, respiratory infections and otitis media.[6,7]

Therefore, allergic rhinitis represents a large global public health burden and is associated with significant healthcare costs. As in adults, the aim of current allergic rhinitis therapies for paediatric patients is to treat the subjective symptoms and to improve objective measures of the disease and other comorbid disorders;[8] however, safety and tolerability have an even greater emphasis.

The safety and tolerability of treatments for paediatric allergic rhinitis are discussed in this review, with a focus on the first-line treatments of oral antihistamines and intranasal corticosteroids. Comprehensive literature searches were conducted in PubMed, from 1980 to January 2003. The key words used for the oral antihistamine section were: 'children', 'allergic rhinitis', and 'oral antihistamines'. All randomised, controlled trials for children <12 years old were identified for the currently available antihistamines, which are approved for use in children, i.e. loratadine, cetirizine and fexofenadine. For the intranasal corticosteroid section, the following keywords were used: '(intra)nasal', '(gluco)corticosteroids', 'growth', 'children', 'allergic rhinitis', 'hypothalamic pituitary adrenal axis', 'beclomethasone dipropionate', 'budesonide', 'flunisolide', 'fluticasone propionate', 'mometasone furoate' and 'triamcinolone acetonide'. The section on other treatments was based on information from two consensus papers[2,9] on allergic rhinitis treatments and supplemented with further information from PubMed searches. A full review of the other available treatments for allergic rhinitis is beyond the scope of this article.

1. Allergic Rhinitis Guidelines

The European Academy of Allergology and Clinical Immunology (EAACI) consensus statement on the treatment of allergic rhinitis, and the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines have both been developed by expert panels. The ARIA guidelines were also developed in collaboration with the WHO, according to the evidence-based medicine method. These guidelines indicate that management of allergic rhinitis (both intermittent and persistent) in children should follow the same principles as in adults, with adaptation of doses and special considerations regarding adverse effects.[2,9] However, few drug treatments are approved for use in children under the age of 2 years.

Following ARIA recommendations, allergen avoidance is considered the first step in allergic rhinitis management, followed by environmental control; however, the evidence for the effectiveness of these procedures is limited. Subsequent pharmacotherapy recommendations are evidence-based; depending on symptom severity, oral or local antihistamines are mainstay treatments for paediatric intermittent disease and the mild persistent condition. Nasal chromone use is also common.[2,9] In the case of moderate-to-severe persistent rhinitis, or if symptoms are not adequately controlled despite the use of environmental control and/or oral or local antihistamines or chromones, intranasal corticosteroids are recommended, followed by the combination of antihistamines and corticosteroids. Immunotherapy should be considered in children,[9] and oral or intranasal decongestants and intranasal anticholinergics are also recommended.[2]

The guidelines express concern over the possible effect of some intranasal corticosteroids on growth and the need for monitoring children while receiving intranasal corticosteroid therapy. In addition, oral and intramuscular corticosteroids should always be avoided in young children. The use of non-sedating antihistamines is recommended in children to prevent the cognitive impairment seen with first-generation, and some second-generation, antihistamines.[2,9]

2. Oral Antihistamines

The effects of histamine are mediated through four pharmacologically distinct subtypes of histamine receptors, H_1 to H_4, which are all members of the G protein-coupled receptor family. The H_1 receptor is distributed in the brain, smooth muscle cells, endothelial cells, adrenal medulla and heart, and plays a role in smooth muscle contraction, stimulation of nitric oxide formation, endothelial cell contraction and increased vascular permeability, all of which are closely involved in allergic conditions.

In contrast, the H_2 receptor is expressed in gastric cells, cardiac tissues, smooth muscle cells and immune cells, and only moderately in the brain; antagonists of this receptor have proven to be effective for acid peptic disorder of the gastrointestinal tract.

First-generation H_1 antihistamines, although effective in relieving the symptoms of rhinitis and urticaria, are associated with unwanted adverse effects, such as sedation and impairment of psychomotor function, due to a lack of H_1 receptor selectivity and, in particular, their penetration into the CNS.

Few studies have assessed the incidence of adverse effects of first-generation antihistamines in children. However, reports of severe adverse reactions and deaths following overdoses of first-generation antihistamines in paediatric patients have been published.[10-13] Despite the lack of adequate studies in children and infants, many of the old sedating antihistamines are still commonly given to this population.

Newer antihistamines were developed in the early 1980s with the aim of being more specific for the H_1 receptor and of overcoming the adverse effects observed with older agents. These newer agents are the medication of choice in patients with mild intermittent allergic rhinitis. However, issues of receptor selectivity and the potential for CNS adverse effects still remain with some of these agents. For example, when administered at recommended doses, cetirizine has been associated with sedative effects.[14] The safety and efficacy of H_1 antihistamines in allergic rhinitis have been assessed in several paediatric studies. For children <12 years of age, three newer oral antihistamines are currently approved: cetirizine, loratadine and fexofenadine. Some of the newer antihistamines could also have antiasthmatic activity[15,16] and have been shown to be safe for use in children with asthma. Indeed, studies have shown that cetirizine is beneficial in delaying or preventing the inception of asthma symptoms in subgroups of infants and toddlers with atopic dermatitis sensitised to grass pollen, house dust mite, or both.[17]

2.1 Clinical Studies

Fexofenadine has been examined in double-blind controlled studies in children with seasonal allergic rhinitis aged 6–11 years and found to be effective and well-tolerated.[18,19] In a 2-week, double-blind, randomised, placebo-controlled study of 875 children, oral fexofenadine 15, 30 and 60mg twice daily showed no dose-related trends in adverse effects, with a demonstrated safety profile similar to that of placebo.[18] Cetirizine has been evaluated in doses ranging from 2.5mg to 10mg in double-blind studies in children aged 2 years and older, and was shown to be effective and well tolerated.[20-22] In children aged 6–11 years, the major adverse effect with cetirizine was abdominal pain in 4.4% receiving 5mg and 5.6% receiving 10mg compared with 1.9% in the placebo group. A long-term safety study performed in 817 very young children with atopic dermatitis (aged 12–24 months at study entry) has also demonstrated the safety of cetirizine in this population.[23] The safety and efficacy of loratadine (5mg and 10mg) was evaluated in a randomised, parallel-group study in 96 children with seasonal allergic rhinitis aged 3–6 years. The frequency of adverse effects was found to be low and comparable with placebo.[24]

2.2 Cardiotoxicity

Over the past few years, evidence has emerged that some antihistamines are potentially cardiotoxic.[2,25] This has been attributed to their low selectivity for the H_1 receptor.

2.2.1 Tachycardia

Older-generation antihistamines were associated with adverse effects, including dry mouth and urinary retention, as a result of blockade of muscarinic cholinergic receptors. The H_1 receptor shares close sequence homology with the muscarinic M_1 to M_5 receptors. Studies have shown that the M_1 receptor has a role in memory function and is located in the CNS and ganglia, whereas the M_3 receptor is located on glandular and smooth muscle cells. The M_2 subtype is involved in maintaining vagal tone and blockade of this receptor is linked with tachycardia.

In vitro binding studies have led to a greater understanding of the cardiac effects of different antihistamines and have shown that this activity is separate from H_1 antihistaminic potency and is, therefore, not class-related. For example, *in vitro* binding studies using fexofenadine and desloratadine to compare their affinities for, and effects on, all five muscarinic receptor subtypes and the H_1 receptor[26] have shown that fexofenadine is 600-fold more selective for the H_1 receptor compared with the M_2 receptor. In contrast, desloratadine is only 5-fold more selective for the H_1 receptor compared with M_2 receptors.[26] In addition, desloratadine was shown in a recent study to increase the resting heart rate of conscious dogs, both under normal conditions and following heart failure.[27]

2.2.2 Ventricular Arrhythmia

Some antihistamines can produce prolongation of the corrected QT (QTc) interval due to blockade of the delayed rectifier potassium current (I_K) in the myocardium. Such prolongation of the QTc interval predisposes to ventricular arrhythmias, in particular the life-threatening torsades de pointes. [25,28-31]

The antihistamines astemizole and terfenadine have been linked to prolongation of the QTc interval when administered to patients with hepatic impairment, or concomitantly with drugs that inhibit the cytochrome P450 (CYP) enzyme system (such as ketoconazole and erythromycin).[2,25] Co-administration of these antimicrobial agents has been shown to inhibit CYP-mediated metabolism (particularly CYP3A) of those antihistamines that are metabolised by this pathway, resulting in increases in their serum concentrations. At higher concentrations, these antihistamines can inhibit the delayed rectifier potassium current, resulting in cardiotoxic effects in some patients, such as torsades de pointes.[25,28-31] However, there are significant differences in the metabolic profiles of antihistamines, ranging from those that exhibit significant interactions with CYP isoenzymes (e.g. astemizole and terfenadine) to those that are practically devoid of any metabolic interaction (e.g. fexofenadine, cetirizine and mizolastine). Loratadine and ebastine do undergo metabolism by this system, but evidence shows that they do not block ion channels.[2] The clinical relevance of these increases in plasma concentrations is also dependent on the therapeutic window of the antihistamine. For example, for those antihistamines with a wide therapeutic window, such as fexofenadine, increases in plasma concentrations would not be clinically relevant.

H_1-selective antihistamines have been screened *in vitro* for cardiotoxic potential based on their ability to block the potassium channel encoded by the human ether a-go-go-related gene (HERG), which is thought to represent the basis of the rapid component of the potassium current (I_{Kr}). Fexofenadine has been rigorously assessed in such studies and has been shown to have no inhibitory effect on the HERG channel, even at supratherapeutic doses.[32] Similarly, fexofenadine has been shown to demonstrate only a weak effect on a variety of cloned human potassium ion channels involved in the repolarisation of the myocardium. Cetirizine has also been shown to be devoid of any inhibitory activity on HERG channels.[33] In contrast, tecastemizole and its active metabolite, astemizole, have been shown to block HERG channels when expressed *in vitro* at 1 and 100 nmol/L with IC_{50} values of 0.9 nmol/L and 27.7 nmol/L, respectively.[34] Although the plasma concentrations of tecastemizole required for antihistaminic effects are less than those necessary for blocking HERG channels, the potential for QTc interval prolongation could exist at high drug concentrations. Similarly, a study of the potassium ion channel blocking profile of loratadine and terfenadine showed that both drugs blocked HERG current amplitude;[35] therefore, the potential for QTc interval prolongation could also exist at very high concentrations of these drugs.

The potential cardiac toxicity of H_1 antihistamines such as cetirizine, fexofenadine and loratadine has also been studied prospectively in controlled clinical trials in children with allergic rhinitis, seasonal allergic rhinitis or atopic dermatitis and have been shown to have no effect on the QTc interval (table I).[18,23,36,37] In these studies there were no reports of arrhythmias after administration of the antihistamine. In the prospective, 18-month

Table I. Summary of cardiac safety studies with H_1-selective antihistamines in children with allergic rhinitis or atopic dermatitis (reproduced with permission from Simons,[38] by courtesy of Marcel Dekker Inc.)

Study	Dosage (mg)	Study design	Subjects	Results
Cetirizine[36]	5 or 10 od	28-day study in SAR	123 patients aged 6–11 years: 35 (5mg), 44 (10mg), 40 (placebo)	No prolongation of the QTc interval
Cetirizine[23]	0.25 mg/kg bid (2.5–5.5 bid)	18-month study in atopic dermatitis	795 patients aged 1–3.5 years: 399 (2.5–5.5mg); 396 (placebo)	No prolongation of the QTc interval
Loratadine[37]	5 or 10 od	14-day study in SAR	902 patients aged 6–12 years: 95 (5mg), 232 (10mg), 243 (chlorpheniramine), 332 (placebo)	No prolongation of the QTc interval
Fexofenadine[18]	15, 30, 60 bid	14-day study in SAR	875 patients aged 6–11 years: 224 (15mg), 209 (30mg), 213 (60mg), 229 (placebo)	No prolongation of the QTc interval

bid = twice daily; **od** = once daily; **SAR** = seasonal allergic rhinitis; **QTc** = corrected QT.

Early Treatment of the Atopic Child (ETAC) study,[23] no child receiving cetirizine therapy had an increase in the QTc interval. Similarly, in children with seasonal allergic rhinitis, ECG readings showed that fexofenadine had no effect on the QTc interval.[18] In contrast, the cardiotoxicity of levocetirizine, mizolastine and tecastemizole remains to be fully established.

2.3 Sedation and Impairment

Histamine has been widely reported to play an important role in maintaining CNS arousal and alertness. Therefore, antihistamines that cross the blood-brain barrier and antagonise H_1 receptors in the brain can produce impairment of cognitive function, including attention, memory, sensorimotor coordination, information processing and psychomotor performance.[39,40] In infants and young children, stimulatory effects of first-generation H_1 antihistamines on the CNS have also been shown to result in irritability, nervousness, hyperactivity and seizures.[41,42] Data from studies using first-generation antihistamines demonstrated significant adverse effects as a result of their sedative properties, producing impairment of cognitive and academic function in children.[43,44]

The rigorous testing of antihistamines to ensure the CNS safety of these agents is a relatively recent development. Penetration into the CNS in adults can be measured objectively using psychometric tests, developed specifically to assess the central effects of drugs, and also by positron emission tomography (PET) imaging. In adults, a lack of sedation has been shown for most of the newer compounds at therapeutic doses; however, many have not been studied at higher than recommended doses and those that have, such as cetirizine, have shown dose-related increases in somnolence.[45] A meta-analysis of published data on antihistamines has shown that in 31 objective and subjective impairment tests, fexofenadine (at doses up to 240mg in clinical studies) was not associated with any sedation or impairment, with an impairment/non-impairment ratio of zero.[14] In addition, a recent study has also shown the lack of impairment with fexofenadine at doses up to 360mg.[46] In contrast, the meta-analysis revealed that other second-generation antihistamines, such as mizolastine, loratadine and cetirizine, were associated with sedation/impairment in a number of tests in adults, often when used at higher than recommended clinical doses.[14] Recent data indicate that desloratadine at doses of 5, 10 and 20mg may not be devoid of CNS adverse effects and suggest that further evaluation is required to determine whether this agent is able to cross the blood-brain barrier.[47]

In children, a lack of adverse effects from second-generation H_1 antihistamines has been demonstrated using EEG and psychomotor performance tests.[44,48-50] Long-term treatment with cetirizine does not affect the achievement of developmental benchmarks or behaviour assessed using the Behavioural Screening Questionnaire or psychomotor ability assessed using the McCarthy Scales of Children's Ability.[51] A study of the effects of antihistamines on childrens' learning ability demon-

strated that the first-generation antihistamine diphenhydramine caused significantly more learning impairment compared with loratadine.[43]

Clinical evaluation of somnolence following administration of cetirizine in children with seasonal allergic rhinitis showed that somnolence was reported in 1.9% and 4.2% of patients receiving 5mg and 10mg cetirizine, respectively, compared with 1.3% receiving placebo.[20,21] An efficacy and tolerability study in children aged 3–6 years with seasonal allergic rhinitis showed that loratadine had no effect on somnolence.[24] In a safety study of 875 children with seasonal allergic rhinitis using fexofenadine at doses of 15, 30 and 60mg twice daily, the incidence of somnolence was low (n = 2 for placebo and n = 1 for fexofenadine).[18] Similarly, in a recent study using oral fexofenadine in 935 paediatric subjects aged 6–11 years, no clinically meaningful sedative or other class effects associated with first-generation antihistamines were observed.[19]

3. Intranasal Corticosteroids

Intranasal corticosteroids are the most effective anti-inflammatory agents used for the treatment of paediatric allergic rhinitis; however, the safety of these compounds remains a controversial topic. The safety implications associated with corticosteroids in general are potential long-term, dose-related systemic adverse effects, such as suppression of adrenocortical function, growth and bone metabolism. The intranasal corticosteroids can be absorbed through airway and gastrointestinal routes; most of the dose is swallowed.[52] The extent of these effects is influenced by factors such as corticosteroid type, pharmacokinetic profile, mode of delivery and the delivery device. Topical corticosteroids (inhaled and intranasal) were introduced to reduce the systemic effects seen with long-term use of oral agents, which frequently resulted in growth retardation in children and adolescents.[53]

Adrenal functions can be suppressed with long-term use of corticosteroids, particularly oral use, as a result of suppression of the hypothalamic-pituitary-adrenal (HPA) axis activity. If corticosteroid treatment is stopped abruptly or in stressful conditions where the adrenal gland is unable to respond, acute adrenal insufficiency may result.[53] Childhood growth and, therefore, the assessment of drug effects on growth, is complex due to natural changes in growth regulation and the timing and rate of growth and pubertal development.[52] The exact mechanism by which corticosteroids inhibit linear growth is unknown, although a number of effects including inhibition of growth hormone release, inhibition of insulin-like growth factor-1 bioactivity, and direct suppression of the multiplication and differentiation of cartilage cells and collagen synthesis for new bone are involved.[52,53]

HPA axis function tests can be categorised into two types; those that measure the presence of a corticosteroid in the circulation, such as plasma cortisol levels and 24-hour urinary free-cortisol tests; and stimulation tests with corticotropin (adrenocorticotropic hormone), lypressin, and corticotropin-releasing hormone. Measurements of endogenous basal cortisol levels are very sensitive tests, but only indicate the presence of an exogenous corticosteroid in the system and do not necessarily indicate a risk of adverse effects. In addition, 24-hour urinary excretion of total or free cortisol is widely considered a more sensitive and appropriate measurement than morning cortisol tests. Stimulation tests, although less sensitive to the presence of corticosteroid, are more indicative of a clinical effect on function as they can be used to determine the function of the HPA axis, e.g. the corticotropin test measures the capacity of the adrenal gland to secrete cortisol.[52-54] It is also important to note that the conventional high-dose tetracosactide (cosyntropin) test is supraphysiological (250μg) and, therefore, less sensitive than the low-dose (0.5μg) test.

Growth studies are more indicative of a clinical effect than adrenal function tests. Short-term studies (<6 months) use knemometry to measure lower leg growth, while stadiometry is a more useful and practical test employed in intermediate-term (6–12 months) and long-term (>12 months) studies. A number of other factors influence the assessment of drug effect, including age and growth pattern, dis-

ease severity, timing of drug administration, doses used, and adherence to treatment.[52]

The intranasal corticosteroids currently approved for use in the treatment of paediatric allergic rhinitis are beclometasone, budesonide, flunisolide, fluticasone propionate, mometasone and triamcinolone. These intranasal corticosteroids are mainly metabolised in the liver, and have a short half-life and rapid first-pass hepatic metabolism.[53] However, the pharmacokinetics of the intranasal corticosteroids do vary quite considerably in terms of their degree of systemic absorption, potency, binding affinity, lipophilicity, volume of distribution, and half-life (ranging from 0.5–3 hours).[53]

Although relatively few studies have been performed with intranasal corticosteroids in children, a number of key studies have indicated that these agents are effective and well-tolerated in paediatric populations, with a similar adverse effect profile to placebo.[55-58] In addition, long-term use does not appear to cause atrophy of the nasal mucosa, and adverse effects, such as crusting, dryness and minor epistaxis, are mild. Septal perforations are also thought to be rare.[2,9] Evidence also suggests that intranasal corticosteroids do not significantly affect growth. However, in the absence of more comprehensive findings, the monitoring of growth in children receiving intranasal corticosteroids should be routine, and guidelines recommend that more data are required on the safety of these corticosteroids in young children.[2,9]

3.1 Adrenal Function Suppression

The effects of intranasal corticosteroids on adrenal gland function have been monitored in a number of clinical studies that have shown that, in general, second-generation intranasal corticosteroids do not appear to suppress the HPA axis at recommended doses (table II).

3.1.1 Presence of Corticosteroid

Budesonide nasal powder (200 and 400μg once daily) did not affect the HPA axis in 83 children and adolescents (aged 4–16 years) with seasonal allergic rhinitis in a 4-week, randomised, double-blind, placebo-controlled study. There was no statistically significant difference between the two budesonide groups and the placebo group in urine cortisol excretion, and no change from baseline in each group in overnight cortisol excretion in the urine.[56]

In a multicentre, double-blind, randomised, placebo-controlled trial involving 250 children aged 4–11 years receiving fluticasone propionate nasal spray 100 or 200μg once daily for 14 days, there was no suppression of HPA at either dose when morning plasma cortisol concentrations were measured.[55] A further double-blind, randomised, placebo-controlled, 4-week study by the Fluticasone Propionate Collaborative Pediatric Working Group confirmed these findings. No suppression of HPA was detected in patients with seasonal allergic rhinitis aged 4–11 years (n = 249) after treatment with fluticasone propionate aqueous nasal spray, measured using morning plasma cortisol concentrations and 24-hour urinary excretion of free cortisol and 17-ketogenic corticosteroids.[59]

In a more recent 2-week, randomised, placebo-controlled, single-blind (fluticasone propionate) or double-blind (triamcinolone) study, treatment with triamcinolone 110 or 220μg once daily did not significantly affect HPA function as assessed by measuring free urinary cortisol, corrected for creatinine clearance. In contrast, fluticasone propionate 200μg once daily significantly decreased the mean urine cortisol/creatinine ratio compared with triamcinolone and placebo.[60]

3.1.2 Stimulation Tests

No suppression of the HPA axis was seen in a study of 20 children aged 7–13 years with perennial allergic rhinitis after 4 weeks of treatment with intranasal beclometasone 400 and 800μg once daily, assessed using lypressin stimulation. In contrast, oral prednisone caused significant suppression of the HPA axis ($p < 0.05$).[54] Similarly, in a double-blind, randomised, placebo-controlled, 1-year trial involving 100 children aged 6–9 years, no suppression of the HPA axis was seen with aqueous beclometasone (168μg twice daily). Normal 8:00am basal cortisol concentrations and normal increases in cortisol concentrations after tetracosactide stimulation (250μg) were reported for all patients.[58]

Table II. Summary of safety assessment studies with intranasal corticosteroids performed in children

Drug	Study design	Subjects	Adrenal function	Growth inhibition
BUD nasal powder (200 and 400μg od)[56]	4-week, R, DB, PC	4–16 years SAR n = 83	No significant difference between BUD and placebo in urine cortisol excretion No changes in cortisol excretion from baseline	
FP nasal spray (100 or 200μg od)[55]	2-week, R, DB, PC, MC	4–11 years SAR n = 250	No significant difference between FP and placebo in morning plasma cortisol concentrations No changes in plasma cortisol from baseline	
FP aqueous nasal spray (100 or 200μg od)[59]	4-week, R, DB, PC	4–11 years SAR n = 249	Morning plasma cortisol concentrations and 24-hour urinary excretion of free cortisol and 17-ketogenic steroids similar across all groups pre- and post-treatment	
TAA (110 or 220μg); FP (200μg od)[60]	2-week, R, DB (TAA) or SB (FP), PC	7.2 years (mean) AR n = 59	TAA: no significant effect on free urinary cortisol corrected for creatinine FP: significantly decreased mean urine cortisol/creatinine ratio compared with TAA and placebo	KM: no clinically significant short-term effect on linear lower leg growth with TAA or FP
BDP (400 and 800μg od)[54]	4-week, R (prednisone positive control)	7–13 years PAR n = 20	No statistically significant difference between basal serum cortisol levels pre- and post-treatment After LVP stimulation there were no differences pre- and post-treatment	
BDP aqueous (168μg bid)[58]	1-year, R, DB, PC	6–9 years PAR n = 100	Normal 8am basal cortisol concentrations Normal increases in cortisol concentrations after tetracosactide stimulation	SM: rate of growth of BDP-treated patients was significantly slower than that of those receiving placebo (primarily attributable to treatment)
MF aqueous nasal spray (50, 100 or 200μg od)[61]	1- or 2-week, R, SB, PC, PG	3–12 years AR n = 96	No significant reductions in plasma cortisol or 24-hour urinary free-cortisol concentrations A normal response to tetracosactide stimulation (assessed in 3–5 year olds)	
MF nasal spray (25, 100 or 200μg od) BDP (84μg bid)[62]	4-week, R, DB, PC	6–11 years SAR n = 679	Basal mean cortisol levels did not differ pre-and post-treatment Response to tetracosactide stimulation was normal pre- and post-treatment	
MF nasal spray (100μg od)[57]	1-year, R, DB, PC, MC	3–9 years PAR n = 98	All patients had a normal response to tetracosactide stimulation at all time-points	SM: no suppression of growth – no difference in the rate of growth compared with placebo (adjusted mean increase in height from baseline greater with MFNS compared with placebo)

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Table II. Contd

Drug	Study design	Subjects	Adrenal function	Growth inhibition
TAA aqueous nasal spray (220 or 440μg od)[63]	6-week, R, DB, PC, MC	6–12 years AR n = 80	Basal mean cortisol levels did not differ pre-and post-treatment Response to tetracosactide stimulation was normal pre- and post-treatment	
BUD aerosol spray (200μg bid)[64]	6-week, R, DB, PG (also terfenadine and methylprednisolone acetate)	6–15 years SAR n = 44		KM: lower leg growth suppressed by BUD
BUD intranasal dry-powder (200 and 400μg od)[65]	4-week, R, DB, PG	7–15 years AR n = 38		KM: did not suppress lower leg growth velocity
MF (100 or 200μg od); BUD (400μg od) aqueous nasal sprays[66]	R, DB, PC, CO	7–12 years AR n = 22		KM: did not inhibit linear lower leg growth rates
BDP aqueous intranasal (median dosage 168μg bid)[67]	Clinical experience study Average duration of therapy: 36 months	2–10 years (at treatment initiation) n = 60		SM: no growth suppression (authors recommend height assessments performed every 6 months)

AR = allergic rhinitis; **BDP** = beclometasone; **bid** = twice daily; **BUD** = budesonide; **CO** = crossover; **DB** = double-blind; **FP** = fluticasone propionate; **KM** = knemometry; **LVP** = lypressin; **MC** = multicentre; **MF** = mometasone; **od** = once daily; **PAR** = perennial allergic rhinitis; **PC** = placebo-controlled; **PG** = parallel-group; **R** = randomised; **SAR** = seasonal allergic rhinitis; **SB** = single-blind; **SM** = stadiometry; **TAA** = triamcinolone.

However, the lack of suppression observed with these tests may be due to their lack of sensitivity; in the same study, growth suppression was observed (see section 3.2).

Studies investigating mometasone aqueous nasal spray have also reported no suppression of the HPA axis. In a randomised, single-blind, placebo-controlled, parallel-group study, 96 paediatric patients aged 3–12 years received mometasone nasal spray 50, 100 or 200μg once daily or placebo for 7 or 14 days. Results indicated no significant reductions in plasma cortisol or 24-hour urinary free-cortisol concentrations, and a normal response to tetracosactide stimulation (assessed in 3- to 5-year-olds).[61]

These results were confirmed in a larger, 4-week, randomised, double-blind study of 679 children aged 6–11 years with seasonal allergic rhinitis.[62] Patients received mometasone aqueous nasal spray 25, 100 or 200μg once daily, beclometasone 84μg twice daily, or placebo. No HPA axis suppression was detected with mometasone at doses up to 200μg, as measured by tetracosactide stimulation. Similarly, a long-term multicentre, double-blind, randomised, placebo-controlled study of 98 children with perennial allergic rhinitis aged 3–9 years receiving mometasone nasal spray 100μg once daily for 1 year reported no effect of mometasone on the HPA axis at any time-point, as assessed via tetracosactide stimulation testing.[57]

No HPA suppression was seen with triamcinolone aqueous nasal spray (220 or 440μg once daily) in a multicentre, double-blind, randomised, placebo-controlled, 6-week study of 80 children with allergic rhinitis aged 6–12 years, measured by tetracosactide stimulation. No significant difference was found between pre- and post-treatment mean plasma cortisol levels.[63]

3.2 Growth Inhibition

The effects of intranasal corticosteroids on growth have been monitored in a number of clinical studies, with mixed results (table II). No studies have been performed to date investigating the final height in children with allergic rhinitis after intranasal corticosteroid treatment.

3.2.1 Knemometry Studies

Studies investigating budesonide have shown mixed results. A study in 44 children with seasonal allergic rhinitis showed that lower leg growth was suppressed after 6 weeks of treatment with budesonide aerosol spray 200μg twice daily and intramuscular methylprednisolone acetate 60mg.[64] However, in a further study by the same investigators, intranasal dry-powder budesonide (200 and 400μg once daily) did not suppress growth in 38 children aged 7–15 years with allergic rhinitis,[65] which may reflect the different modes of delivery or timing of the doses.

In two comparative studies, no effect on growth was seen with any of the intranasal corticosteroids investigated. A short-term study showed that at clinically relevant doses, mometasone (100 or 200μg once daily) and budesonide (400μg once daily) aqueous nasal sprays did not inhibit linear lower leg growth rates.[66] Similarly, no clinically significant short-term effect on linear lower leg growth was seen in children treated with triamcinolone or fluticasone propionate in a randomised, double-blind, crossover study, despite the significant decrease observed in the mean urine cortisol/creatinine ratio with fluticasone propionate compared with triamcinolone and placebo.[60]

3.2.2 Stadiometry Studies

Despite finding no effect on HPA axis function, Skoner et al. discovered growth suppression in 100 children treated with beclometasone 168μg twice daily for 1 year.[58] In this double-blind, randomised, placebo-controlled trial, the rate of growth of beclometasone-treated patients was significantly slower than that of patients receiving placebo. Analysis of normalised heights confirmed that the difference was primarily attributable to the treatment; however, the effect on final height is unknown. Importantly, a recent clinical experience study reporting the effect of beclometasone on medium- and long-term growth showed that aqueous intranasal beclometasone (median dosage 168μg twice daily) is not associated with growth suppression. The records of 60 children aged 2–10 years at treatment initiation, with an average duration of therapy of 36 months and at least two height measurements annually (stadiometry or physician's scale height rod) after therapy initiation, were reviewed.[67] However, the authors recommended that height assessments should be performed every 6 months as some children may be at special risk.

No suppression of growth was seen in 98 children aged 3–9 years treated for 1 year with mometasone aqueous nasal spray 100μg once daily, supporting the lack of effect seen on HPA functions in this study.[57] The mean heights were similar for both treatment groups at all time-points although the adjusted mean increase in height from baseline was significantly greater in the mometasone-treated patients compared with those in the placebo group. However, analysis of the rate of growth showed no difference between the two treatment groups.[57]

A recent double-blind, randomised, placebo-controlled study of fluticasone propionate aqueous nasal spray in children aged 3.5–9 years (n = 150) found no suppression of growth with this intranasal corticosteroid. Equivalent growth velocities and similar increases in height were observed over a 1-year treatment period with fluticasone propionate 200μg once daily and placebo in children with perennial allergic rhinitis. The incidence of adverse events reported as possibly related to study treatment was also similar for both groups.[68]

3.3 Bone Metabolism

Corticosteroids have also been reported to affect bone metabolism, acting on bone formation, sex hormone secretion, calcium absorption and renal calcium reabsorption, leading to osteoporosis.[52] There are few data on bone metabolism in children; however, short-term once-daily administration of intranasal budesonide 200μg, mometasone 200μg and triamcinolone 220μg in 20 adults with allergic rhinitis showed no suppression of osteocalcin, a bone marker of systemic effect.[69] In addition, beclometasone nasal spray had no significant effect on common markers of bone metabolism in a randomised, controlled study of 39 children for 2 months.[70]

3.4 Intranasal Corticosteroid Management

There is a high co-morbidity of asthma and allergic rhinitis, and patients receiving concomitant treatment for both conditions are at higher risk from the adverse effects associated with corticosteroids; the use of inhaled and intranasal corticosteroids may result in greater systemic exposure.[9,52,71] In these cases, use of alternative treatments to reduce corticosteroid load should be considered. In addition, morning administration of intranasal corticosteroids reduces the potential effect on the HPA axis and a once-daily dosage regimen can reduce systemic corticosteroid exposure compared with a twice-daily regimen.[52] The lowest dose required for effective therapy should be used. As with all intranasal and inhaled corticosteroid use, children's growth should be monitored.

4. Other Treatments

Intranasal antihistamines, such as azelastine and levocabastine, can also be used in children. Azelastine is indicated for use in children aged 5−12 years and has been shown to be effective and well-tolerated in children with allergic rhinitis.[72] Azelastine nasal spray can be considered as an alternative to intranasal corticosteroids in patients with persistent, severe symptoms.[4] However, azelastine has been reported to have a bitter taste and a higher incidence of somnolence compared with placebo (11.5% versus 5.4% for somnolence, respectively).[73]

The local chromones, sodium cromoglicate (cromolyn sodium) and nedocromil, appear to be safe and devoid of adverse effects and are commonly used for allergic rhinitis in children.[2,9] However, they have limited efficacy and multiple daily administration is required, therefore, they are only recommended in mild and early rhinitis or for prophylaxis of a known imminent exposure.[9]

In general, topical decongestants should only be used in the short-term as prolonged use is associated with tachyphylaxis, rebound swelling of the nasal mucosa and rhinitis medicamentosa.[9,74] In children under 1 year of age, decongestants should be used with care as they have a narrow therapeutic window, and therefore, may be associated with safety concerns at higher doses. Pseudoephedrine, in particular, is not advised for use in children under 1 year of age.[9]

Ipratropium bromide spray, an intranasal anticholinergic, can be used as intermittent therapy for mild paediatric allergic rhinitis or as add-on therapy in more severe cases.[74] Adverse effects include nasal dryness, irritation, burning, congestion, dry mouth and headache, and are the same in children and adults.[9] Systemic adverse effects are rare, although they do occur at doses higher than 400 μg/day.[9]

Allergen immunotherapy is currently recommended for the treatment of persistent rhinitis, especially more severe forms of the disease. Recently an expert panel convened by the WHO addressed the clinical efficacy of allergen immunotherapy in the treatment of allergic rhinitis induced by pollen or perennial allergens, such as house dust mites. Children were shown to respond better than adults to immunotherapy, particularly in the treatment of asthma. Traditionally, allergen immunotherapy is administered subcutaneously, but recent evidence has stressed the effectiveness of other forms of allergen-specific immunotherapy.[75] The clinical efficacy of local (nasal) and sublingual-swallow immunotherapy (SLIT) have been well-documented, with SLIT facilitating the administration of allergen-specific vaccines in children with allergic rhinitis;[76] however, the efficacy of oral immunotherapy has been found to be inconsistent.

Specific immunotherapy appears to modify the natural history of allergic diseases, preventing new sensitisations from occurring in monosensitised patients.[77,78] More recently, specific immunotherapy has been shown to prevent the onset of asthma in children with allergic rhinitis,[79] and can be used in children aged ≥5 years.[2] Immunotherapy carries a low risk of systemic anaphylactic reaction[9] so treatment must be performed by trained specialists and patients should be monitored for 20 minutes after injection.[2]

Antileukotrienes used alone and in combination with antihistamines to target two key mediators of allergic rhinitis are also potentially beneficial and

have shown good safety profiles in children with asthma. However, efficacy studies have provided mixed results. Montelukast alone has been shown to be significantly better than placebo at controlling the symptoms of rhinitis and also at improving symptoms and quality of life of associated conjunctivitis,[80] and has recently been approved for use in seasonal allergic rhinitis. Furthermore, some combinations (montelukast and cetirizine) have shown equivalent efficacy to intranasal corticosteroids at reducing nasal symptoms.[81] In contrast, a recent study showed that fluticasone propionate aqueous nasal spray was more effective than the combination of montelukast and loratadine, and montelukast alone, in the reduction of pollen-induced nasal eosinophilic inflammation and the control of nasal symptoms in patients with seasonal allergic rhinitis.[82] The additional benefits of antileukotriene and antihistamine combinations have also been put into question by another recent study showing that fexofenadine monotherapy was equally effective as montelukast plus loratadine; both treatments significantly improved the average daily nasal peak inspiratory flow and significantly reduced seasonal allergic rhinitis symptoms, including nasal blockage, compared with placebo.[83]

5. Future Perspectives

There are currently a number of clinical programmes investigating novel modes of action and therapies in allergic rhinitis and asthma. However, to be of any benefit in allergic rhinitis, a new therapy would need to show greater efficacy than the existing first-line treatments, H_1 antihistamines and intranasal corticosteroids, while maintaining safety. There remains a need for new, safer corticosteroids that can be given at high enough dosages to maximise efficacy whilst retaining safety.

Although immunotherapy is currently only available for more severe disease, it is likely that with increased use and experience and improved allergen vaccines, it will become more common practice in milder disease states due to its ability to modify disease expression. Moreover, new forms of immunotherapy are currently being studied, such as CpG motif-conjugated allergens or peptide immunotherapy. Omalizumab, a humanised anti-IgE monoclonal antibody, has been shown to be significantly more effective than placebo in both asthma and rhinitis.[84] It has been indicated that these agents do not generate immune responses,[85] and no serious adverse events have been seen in over 3000 patients treated with omalizumab for up to 1 year.[2]

Potential treatments based on the inhibition of eosinophilic and allergic inflammation are also being developed, including monoclonal antibodies against interleukin (IL)-5, soluble IL-4 receptors, blockade of the serine protease, tryptase, and platelet-activating factor antagonists.[2,85]

6. Conclusion

There are a number of treatment options available for paediatric allergic rhinitis. However, the proven efficacy and good safety profiles of the currently available newer oral antihistamines and intranasal corticosteroids place them as first-line treatments. The wealth of evidence suggests that they are also safe for use in children.

In general, the newer oral antihistamines provide excellent efficacy with few adverse effects. However, it is important to note that differences exist between agents in this drug class. The prolongation of the QTc interval under certain conditions, seen with terfenadine and astemizole, led to the withdrawal of these antihistamines, but this effect has not been repeated clinically with the currently available H_1 receptor antagonists. In addition, few of the non-sedating antihistamines appear to be truly non-impairing at higher than recommended doses, which may be an issue when patients self-dose. Currently, fexofenadine is the only available antihistamine known to be truly non-impairing even at higher than recommended doses. Antihistamines also differ in terms of the range of their therapeutic index, with some being wide enough to continue being safe despite increases in plasma concentrations.

Similarly, newer intranasal corticosteroids appear to be well-tolerated and the evidence suggests that any associated risks appear to be limited and transient, and that these are outweighed by the bene-

fits. However, extensive long-term studies involving final height measurements have not yet been performed; it is, therefore, recommended that the lowest effective intranasal corticosteroids dose is used for long-term treatment and that growth is regularly monitored in children receiving intranasal corticosteroids. For this purpose it should be noted that the assessment of growth suppression appears to be a more sensitive measurement than HPA suppression. In addition, it is important to recognise that the risk of systemic effects may increase in patients treated with inhaled corticosteroids for concomitant asthma and these patients need to be managed accordingly. As a reference, a recent systematic review and analysis of the literature revealed that inhaled corticosteroids exhibited systemic adverse effects at high doses; fluticasone propionate exhibited greater dose-related systemic bioactivity compared with other available inhaled corticosteroids, particularly at doses above 800μg once daily.[86]

Other treatments may also be helpful in managing paediatric allergic rhinitis, and therapies should be considered on an individual basis. Although treatments such as local chromones and ipratropium bromide spray have excellent safety profiles for use in children, they have limited efficacy. Conversely, immunotherapy is a very promising treatment that, with improved allergen vaccines and increased specialist experience, may be used to modify the disease in children in the future.

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