The use of antihistamines in children

Katherine Anagnostou
Kate E Swan
Helen Brough

Abstract

Antihistamines are commonly used in paediatric medicine mainly for the treatment of allergic conditions. First generation antihistamines have been in use for many years, despite limited research studies supporting their use. Second generation antihistamines have been investigated for both efficacy and safety in paediatrics. An optimal understanding of their effects and pharmacology are required for optimal use in each patient. In this review we discuss the indications for use, as well as efficacy and safety of both old and newer antihistamines for the paediatric population.

Keywords allergic rhinitis; antihistamines; asthma; atopic dermatitis; children; urticaria

Introduction

Antihistamines are widely used in paediatrics for the treatment of a variety of conditions, including acute allergic reactions, allergic rhinitis, allergic conjunctivitis, allergic asthma, urticaria and atopic dermatitis. A study by the Spanish Society of Allergology and Clinical Immunology has shown that 56.4% of paediatric patients below the age of 14 years had received some antihistamine before seeing an allergist.

First generation antihistamines have been used for over 50 years and still remain popular, despite the fact that they have not been adequately studied in the paediatric population. In contrast, newer antihistamines (2nd generation) have been studied extensively regarding both their efficacy and safety profile in children. Second generation antihistamines are the treatment of choice for allergic conditions and appear to be safer and less sedative than first generation antihistamines. They also have the added advantage of a longer half-life and less frequent dosing requirements (Table 1).

Antihistamines available for use in paediatrics

There are four types of histamine receptors (H1–H4), of which H1 and H2 receptors stimulate both the early-phase (vasodilation with erythema, angioedema and hypotension) and late-phase allergic response (induction of a pro-inflammatory state through up-regulation of cytokines and cell adhesion molecules). Antihistamines do not block H1-receptors as previously thought, but function as reverse agonists. They have a preferential affinity for the inactive state of the histamine H1-receptors and stabilise them in this conformation. As a result of this action, there is a shift in equilibrium towards the inactive state and consequent down-regulation of acute and chronic allergic inflammation.

First generation (old) antihistamines are well absorbed after oral administration and reach peak level concentrations in the serum within 1–3 hours. They can also be administered via the parenteral route for the treatment of anaphylaxis. They are rapidly eliminated in children and generally have shorter half-life and shorter duration of action in the paediatric population compared with adults. However, it takes approximately 3 days for skin reactivity to return to baseline after ingestion. First generation antihistamines are able to cross the blood–brain barrier and as a result, they exert significant effects on the nervous system. They also display anticholinergic effects, such as dry mouth and constipation, via their action through cholinergic receptors.

Second generation (newer) antihistamines commonly used include loratadine, desloratadine, cetirizine, levocetirizine and fexofenadine. Loratadine is rapidly absorbed by the GI tract with a mean half-life of 7.8–11 hours. It is metabolised by the cytochrome P-450 enzyme system in the liver. In contrast, cetirizine, levocetirizine and fexofenadine are largely eliminated without metabolic transformation; subsequently, cetirizine and levocetirizine are excreted in the urine and fexofenadine in the bile. The mean elimination half-life for fexofenadine is 18 hours in children (versus 14 hours in adults), but children attain higher levels of the drug. Most of the newer generation antihistamines have a duration of action of at least 24 hours, facilitating daily dosing. Although plasma clearance of long acting anti-histamine may be less than 24 hours, the medication remains in the extravascular space for longer, with a prolonged effect beyond one day. Regular second generation antihistamines have a more sustained effect, which is still significant 3 days after stopping the medication, compared to placebo. Studies have confirmed that 2nd generation antihistamines also have rapid onset of action, with Cetirizine resulting in inhibited wheal responses within 90 minutes of a single dose, in over 40% of patients. Second generation antihistamines are the treatment of choice for an allergic response due to their high selectivity for the H1 receptor, high efficacy and few side effects.

Clinically, patients are advised to stop taking long-acting antihistamines 5–7 days before skin prick testing and short-acting antihistamine 48 hours prior to testing. The H2 antagonist, ranitidine, has been shown to reduce skin reactivity and there are some suggestions that it should be stopped on the day of testing, however, the clinical significance is not clear.

Indications for use of antihistamines in paediatrics

Allergic rhinitis and conjunctivitis

Allergic rhinitis (AR) is a common chronic childhood disorder and its prevalence is increasing, especially in the Western world.

Katherine Anagnostou *MD (Hons) MSc PhD is a Consultant in Paediatric Allergy, Paediatric Allergy Department, St Thomas' Hospital, London, UK. Conflicts of interest: none declared.*

Kate E Swan *MSc (Allergy) MA BMBCh MRCPCH is a Paediatric Allergy Specialist Trainee (ST8) in the Paediatric Allergy Department, St Thomas' Hospital, London, UK. Conflicts of interest: none declared.*

Helen Brough *MA (Hons) MSc (Allergy) PhD MB BS FRCPCH is a Consultant in Paediatric Allergy, Paediatric Allergy Department, St Thomas' Hospital, London, UK. Conflicts of interest: none declared.*

Commonly used first and second generation antihistamines and route of administration (in brackets)

First generation	Second generation
Chlorphenamine (oral, IV)	Cetirizine (oral)
Hydroxyzine (oral)	Levocetirizine (oral)
Promethazine hydrochloride (oral)	Loratadine (oral)
Ketotifen (oral, eye drops)	Desloratadine (oral)
	Fexofenadine (oral)
	Azelastine (intranasal)
	Olopatadine (eye drops)

Table 1

Symptoms can be troublesome for the child causing significant reduction in quality of life.

Both old and newer generation antihistamines have been used for the treatment of allergic rhinitis. Clinical studies examining the use of first generation antihistamines in children are lacking. However, in 2009, a Global Allergy and Asthma European Network (GA2LEN) position paper examined the risks of these antihistamines and determined that they reduce rapid eye movement (REM)-sleep, impair learning and reduce work efficiency, which can have a significant compounding impact on paediatric patients who already have reduced quality of sleep and poor daytime concentration due to their AR symptoms. In 2007, a case-control analysis of 1834 students in the UK, aged 15 to 17, revealed that up to 43% suffered from AR and that symptomatic allergic rhinitis and resultant medication use was associated with a 70% increased risk of unexpectedly dropping a grade in summer examinations, compared to a 40% risk in untreated students with AR. GA2LEN and Allergic Rhinitis and its Impact on Asthma (ARIA) initiative recommend that older first-generation H1-antihistamines should no longer be available as over-the-counter drugs for self-medication of allergic diseases, with the newer second generation non-sedating H1-antihistamines, which have fewer side effects, being treatment of choice for AR.

There are a large number of studies supporting the use of second generation antihistamines in the paediatric population. Antihistamines are effective in alleviating sneezing, itching and rhinorrhoea; they appear to be less effective against nasal blockage. Specifically, the use of Loratadine, at a dose of 2.5—5 mg daily has shown to improve significantly both nasal and ocular symptoms in a study of 21 children suffering from seasonal allergic rhinitis (hayfever). Several placebo-controlled trials support the use of cetirizine for both seasonal and perennial allergic rhinitis. Children receiving cetirizine daily at a dose of 5 mg BD (twice daily) or 10 mg OD (once daily), have demonstrated significant improvement in their allergic symptoms, compared with the placebo group. In addition, a multi-centre, prospective, randomised controlled study involving 935 children between 6 and 11 years of age has shown Fexofenadine to be significantly superior to placebo in alleviating seasonal allergic rhinitis symptoms with a good safety profile. Some evidence exists that regular use of H1 antihistamines is more effective in controlling symptoms of allergic rhinitis than an ad-hoc regimen. A continual, long-term treatment may result in better control of airway symptoms and improved quality of life.

Topical nasal antihistamine azelastine is more effective in treating allergic rhinitis symptoms than oral antihistamines, but intranasal steroids are far superior to antihistamine monotherapy for allergic rhinitis. A combination of an intranasal steroid and antihistamine spray also demonstrates good efficacy, with some evidence that it is better than either intranasal steroid or topical nasal antihistamine alone. For allergic conjunctivitis, olopatadine eye drops have shown good effectiveness and symptom relief.

Allergic asthma (in combination with allergic rhinitis symptoms)

Most children with asthma, also have allergic rhinitis. The concept of the "united airway" has been in the literature for several years and it is known that upper airway disease (rhinitis) often precedes lower airway disease (asthma). Immunomodulatory cytokines, produced as a result of allergic activation of mast cells in the nasal mucosa, can cause an inflammatory response in the lower airways. Histamine is an important inflammatory mediator in the respiratory tract and a rise in plasma levels has been noted in asthma attacks. Antihistamines have been shown to improve cough and lung function in children with pollen allergy, during the pollen season, as one would expect with the concept of the "united airway". A systematic review has indicated that ketotifen alone or in combination with other drugs effectively improved asthma and wheezing control in children with mild to moderate asthma. Generally, in patients with both upper and lower airway inflammation (concurrent symptoms of rhinitis and asthma), the use of antihistamines may induce a significant decrease in symptoms as well as in the use of bronchodilators. A population-based, case-control study in patients with asthma and allergic rhinitis in the USA suggested that treatment of allergic rhinitis reduces the risk of emergency room visits and hospitalisations for asthma.

Studies examining the role of regular antihistamine use in preventing asthma in children sensitised to pollen and house dust mites, have failed to demonstrate a significant difference in asthma prevalence; therefore antihistamines are not recommended for this use. According to the current BTS guidelines, antihistamines should not be used in the management of asthma *per se*.

Urticaria

Antihistamines are regularly used for the treatment of both acute and chronic urticaria in children. Acute urticaria is common and