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NEW TRENDS IN PEDIATRIC ANTIHISTAMINE USE

In recent years, there has been a move away from the use of traditional first-generation antihistamines (AH) in favour of newer, non-sedating antihistamines. These second and third-generation antihistamines have evolved into mainstays of treatment in the treatment of allergic diseases. They are widely used in dermatology in the management of urticaria as well as for multiple off-label uses including pruritus, insect bite reactions, mastocytosis and other mast-cell releasing diseases. They are faster-acting, safer, and more efficacious than traditional first-generation sedating antihistamines[1,2]. There is also growing evidence to support the long-term use of newer generation antihistamines as potential disease-modifiers in the pediatric atopic march from infancy through childhood.

Background

Antihistamines are a class of medication that act as inverse agonists by downregulating the constitutive activated state of the histamine H1 and H2 receptors[3]. Histamine acts on a wide range of target cells in the skin to stimulate the development of allergic-related inflammatory diseases[3].

First generation antihistamines were introduced in the 1940s. These agents such as diphenhydramine (Benadryl®) and hydroxyzine (Atarax®) have poor receptor selectivity and non-specifically bind muscarinic, serotonin, and α-adrenergic receptors, as well as cardiac K+ channels, leading to several intolerable and potentially life-threatening adverse effects[4].

Older, first-generation AHs have significant and common anti-cholinergic side effects including: sedation, cognitive impairment, poor sleep quality, dry mouth, dizziness, orthostatic hypotension and coma[3]. Cardiac adverse events including QT prolongation, torsade de pointes as well as cardiac toxicity pose an increasing concern with the use of first-generation AHs. Despite this evidence, first-generation AHs continue to be over-utilized because of their easy accessibility as an over-the-counter medication and long history of use. Many experts believe they should be used only as a last resort and eventually should be available only behind the counter in pharmacies[4].

In Canada however, online surveys of physicians and pharmacists show that Benadryl© (diphenhydramine) remains the most recommended antihistamine for allergic symptoms in children in each of the last 7 years[5]. This paradox has led to a position statement

from the Canadian Society of Allergy and Clinical Immunology (CSACI) stating that "newer generation H1-antihistamines are safer than first-generation H1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria[4]".

Pharmacokinetics

High-quality trials have demonstrated that newer generation AHs are superior in safety compared to older first-generation AHs. On average, the newer agents also have improved potency, efficacy, and duration of action[1,2]. These agents also have a high therapeutic index; that is, the ratio of the minimum toxic dose and minimum therapeutic dose[3]. In fact, many clinicians use newer-generation antihistamines at double, triple, and even quadruple the labelled dose for certain indications (i.e.: chronic spontaneous urticaria) with excellent efficacy and tolerability[6].

A perceived quicker onset of action of older AHs is often cited as a reason why patients and clinicians choose first-generation medications, however this perception has been proven inaccurate in clinical studies[7]. In a double-blind placebo-controlled trial, both cetirizine and loratadine were found to have significantly faster onset of action, potency, and duration of action when compared to chlorpheniramine[8].

Name Generic (Trade)	Tablet size	Dosing	Peak level, half-life (hours) ,	Side effects
Traditional sedating H1 Antihistamines				
Diphenhydramine hydrochloride (Benadryl)	25, 50 mg Elixer 12.5 mg/ 5 mL	25-50 mg q 6-8h (adult) Pediatric: 1 to 1.5 mg/ kg/dose (Max: 25 to 50 mg/dose) PO 3 to 4 times daily, up to 5 mg/kg/day	0.6-2.8h, half-life=4h	Sedation, hyperexcitability, impaired cognitive function, increased appetite, dry mouth, constipation, dysuria, erectile dysfunction, tachycardia, arrythmias, blurred vision
Hydroxyzine (Atarax)	10, 25, 50, 100 mg Syrup 10 mg/ 5 mL 12.5-25g q 6-8 h	12.5-25 mg q 6-8 h (adult) Pediatric: <6 yo 50 mg po in divided doses 6-12 yo 50-100 mg po in divided doses	1.7-2.5h, half life= 3h	
Low sedation H1 antihistamines				
Bilastine (Blexten)	2.5 mL oral solution 10 mg orodispersible quick melt tablets 20 mg	4-11 yo: 10 mg po QD 12 yo+: 20 mg po QD	0.7-2.6h Half life= 14.5 h	Minimal
Rupatidine (Rupall)		2-11 years Children >35 mg= 5 mL (5 mg of rupatadine) oral solution daily 10-25 kg : 2.5 mL (2.5 mg) daily	0.75-1h, half life= 12-15h	
Cetirizine (Reactine)	5, 10 mg Syrup 5 mg/5 mL	10 mg QD Peds 2-6 years: 5 mL OD or 2.5 mL BID	0.75-1h, half life= 12-15h	
Loratadine (Claritin)	10 mg Syrup 5 mg/mL	10 mg QD	0.7-1.3 h, half life= 2-14 h	
Fexofenadine (Allegra)	60, 120, 180 mg	180 mg QD or 60 mg BID	1-3 h, half life = 19-34h	

Table I: *Current Antihistamines[3]*

Pediatric Early Treatment

A growing body of research supports the short and long-term safety and efficacy of newer generation antihistamines in pediatric populations. There have been several successful dose-finding, safety and interventional studies in patients younger than the current approved age-range. There is also evidence to support the role of antihistamines as an interventional therapy in the progression of the "atopic march". The atopic march has been best described as involving the progression of allergic conditions that have common genetic and environmental predisposing factors, and that share the immunologic feature of one or more allergen-specific T helper type 2 (Th2) responses. Importantly, the presence of one allergic condition increases the risk for the development of others, resulting in the additive feature of the atopic march. Classically, the atopic march begins with atopic dermatitis (AD), and progresses to IgE-mediated food allergy, asthma, and allergic rhinitis. Each of these are conditions carry a complex pathophysiology involving multiple facets of the immune system.[9]

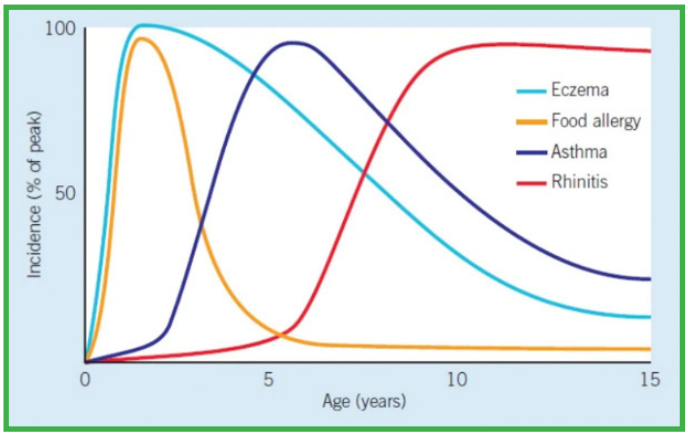

Figure 1: *The Atopic March*[13]

The safety of cetirizine in infants 6-11 months of age was studied in a randomized, double – blind placebo controlled trial[14]. Infants were randomized to receive 0.25 mg/kg of cetirizine orally or a matching placebo twice daily orally for 1 week. The results demonstrated no difference in treatment-related adverse events between the cetirizine and placebo groups (including QT interval). A trend was observed toward fewer adverse events and sleep-related disturbances in the cetirizine group compared with placebo.

The ETAC (Early Treatment of the Atopic Child) study is a multi-country, double-blind, randomised, placebo-controlled trial involving 817 infants with a history of atopic disease in a parent or sibling who were treated for 18 months with either cetirizine (0.25mg/ kg b.i.d.) or placebo to determine whether early intervention in the atopic march can prevent progression from atopic dermatitis to asthma and allergic rhinitis. Researchers have postulated that the anti-allergic properties of newer antihistamines have a positive effect on the development of airway inflammation and asthma in infants with atopic dermatitis[15]. The number of infants who developed asthma was found to be lower in the cetirizine-treated group for those subjects who were sensitized to pollen or house dust mites. The use of cetirizine was shown to be safe with a low incidence of adverse events over the 18-month period. The authors conclude the antihistamine treatment as a primary pharmacological intervention strategy to prevent the development of asthma in specifically sensitized infants with atopic dermatitis.

The conclusion of the ETAC study was confirmed by a recent Cochrane review that evaluated the efficacy of oral H1 antihistamines as an add-on therapy to topical treatment for eczema, highlighting that cetirizine had fewer side effects and less need for additional H1-antihistamines in case of eczema flare compared with other antihistamines used as an add-on therapy[16].

A similar study (EPACC – Early Prevention of Asthma in Atopic Children) evaluated levocetirizine 0.125 mg/ kg vs placebo twice daily for 18 months in 510 atopic children aged 12-24 months[17]. The most frequent adverse events reported were upper respiratory tract infection, transient gastroenteritis symptoms or exacerbations of allergic disease. There were no significant differences between treatment groups in height, mass, attainment of developmental milestones and laboratory tests. Again, there was benefit seen in the prevention of asthma and allergic rhinitis in the treatment group.

The first-generation AHs may occasionally be used for sedation and sleep-inducing qualities. However, there are concerning potential adverse events including a next-day "hang-over" effect, impaired vigilance, divided attention, working memory, sensory-motor performance, and reduced latency to daytime sleep[11]. Older AHs have also been associated with decreased school performance measures. For example, students with symptoms of allergic rhinitis were 40% more likely to drop a grade from practice tests to final examinations and 70% more likely to drop a grade if they reported taking older sedating AHs[12].

In contrast, the ETAC group has evaluated the impact of long-term use of cetirizine on the behavioural, cognitive, and psychomotor development of very young children with atopic dermatitis[18]. Well-validated measures of behaviour (Behaviour Screening Questionnaire) and cognition (McCarthy Scales of Children's Abilities) for patients aged 32-53 months treated with 0.25 mg/kg cetirizine twice daily over 18 months were used in this analysis. There were no significant differences between cetirizine and the placebo group on either behavioural or cognition measures or in psychomotor milestones during or after the study treatment[18]. These findings suggest that there are no adverse effects on behaviour or learning processes associated with prolonged use of cetirizine in young children with atopic dermatitis.

Conclusion

Despite the widespread availability of newer generation AHs, older AHs remain over-utilized. Newer generation AHs are proven to be significantly safer than first-generation AHs, with a faster onset of action, and with superior potency, selectivity and efficacy. There is also growing evidence to support long-term safety and efficacy of these AHs as well as a potential interventional role in the atopic march.

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