

Antihistamine in Pediatrics Dermatology

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Abstract: Antihistamine commonly used in cases of pediatrics dermatology. Skin diseases are generally found in at least 30% of all visits to pediatrics clinics. Pediatrics population is heterogeneous, which range from preterm neonates to adulthood after puberty. Each group has a higher complex physiological, developmental and psychological characteristic than the adult population, this description varies widely from neonates to adulthood. H(1)-antihistamines are generally used to relieve itching and other symptoms due to atopic dermatitis, urticaria, allergic rhinitis, or other diseases that have high morbidity in children. H(1)-antihistamines can be categorized into first-generation and second-generation antihistamines. The first generation H(1)-antihistamines penetrate the blood brain barrier and thus have a significant effect for the central nervous system giving them a sedative effect. The adverse effect of H(1)-antihistamines such as sedation, central nervous system disturbances, gastrointestinal complaints, anticholinergic effect, cardiac arrhythmias, moreover hypersensitivity reactions. Second generation of H(1)-antihistamines are the drugs of choice for allergic responses because of their high selectivity to H1 receptors, high efficacy, and minimal side effects. The half-life in plasma depends on drug metabolism and elimination processes in the body. The process is the same in children and adults, but it is said to occur more rapidly in several cases of children with certain antihistamines. Adverse reaction in children reported against multiple antihistamine administered, although antihistamine is an important drug for use, should not forget that antihistamine also can cause severe reaction and not completely safe drugs.

Keywords: antihistamine, pediatrics, allergy, dermatology

1. Introduction

Antihistamine commonly used in cases of pediatric dermatology [1]. It is widely used for histamine release condition, that present erythema, edema, and itch as skin symptoms [2], [3]. Skin diseases are generally found in at least 30% of all visits to pediatric clinics. Allergic skin disease such as atopic dermatitis and urticaria are the most common cases found [4]. Atopic dermatitis is the most common chronic skin inflammation found in infants and children[5]. Chronic idiopathic urticaria is one of highly severe illnesses to patient quality of life, which its prevalence is increasing [6]. These cases use antihistamines as their main therapy[7]. Most of the case are chronic recidive, so that antihistamine need to give in long term and repeated.

Pediatric population is heterogeneous, which range from preterm neonates to adulthood after puberty. Each group has a higher complex physiological, developmental and psychological characteristic than the adult population, this description varies widely from neonates to adulthood. Simple efficacy and safety measurement from adult approach to child are not sufficient to administer pediatric pharmacotherapy, which lead suboptimal therapy, unwanted responses, and drug side effect reactions[8]. Although lack of basic evidence regarding the use of antihistamines in infants is still limited, most parents, caregivers, and health professionals assume that this drug has been adequately tested and is safe for pediatric uses. This is due to the wide availability of this drug in liquid, including in the form of drops for babies. Where the purchase does not require a prescription, and free to sell in the market[9]. Therefore, we need to consider the safety and efficacy of antihistamine use in paediatrics based on age grouping[10].

2. The Type of H(1)-Antihistamine

H(1)-antihistamines can be categorized into first-generation and second-generation antihistamines [11]. The first generation of H(1)-antihistamines have weak selective bonds to the H(1) receptors, instead they bind strongly to the muscarinic cholinergic α -adrenergic, serotonin receptors, and ion channels [2],[12]. Because of the first generation of H(1)-antihistamine is lipophilic, it can cross the blood-brain barrier to the central nervous system [2], [13]. First-generation H(1)-antihistamines were used to treat nausea (promethazine), migraines (pizotifen) and as pre-operative drugs, but binding with multiple receptors has also resulted in many adverse effects. New H(1)-antihistamines were developed in the 1980s with minimal or non-sedative sedative effects, with minimal penetration to the blood-brain barrier by adding a carboxylic moiety with a protonated amine, reducing the drug's penetration capacity to the blood-brain barrier and increasing the H(1) selectivity. Table 1 shows the chemical and functional classifications of antihistamines [14], [15].

There are four histamine receptors (H1-H4), where the H1 and H2 receptors stimulate the early phase (erythema, angioedema, and hypotension caused by vasodilatation) and the late phase of the allergic response [2], [16]. Antihistamines do not block histamine receptors, but act as reverse agonists [1]. Antihistamines bind to inactive histamine receptors and stabilize the condition. The H(1)-antihistamines can also be administered intravenously, usually for anaphylactic case. H(1)-antihistamines are eliminated rapidly in children, and have a shorter half-life compared to adults. Second generation of H(1)-antihistamines, also called non-sedative antihistamines, have a heavier molecular weight so they do not easily cross the

blood brain barrier [8], [17]. Commonly used second generation of H(1)-antihistamines are loratadine, desloratadine, cetirizine, levocetirizine, and fexofenadine [3], [18]. Second generation of H(1)-antihistamines are the drugs of choice for allergic responses because of their high selectivity to H1 receptors, high efficacy, and minimal side effects [3], [19]. The types of H(1)-antihistamines that

commonly used in pediatric dermatology cases along with their preparations and dosages are described in Table 2 [2], [20], [21].

Table 1: Functional and chemical classification of H(1)-antihistamines [14], [15].

Class	Functional classification	
	First Generation	Second Generation
TYPE I Ethylenediamines	Antazoline, pyrilamine, tripeleennamine	-
TYPE II Ethanolamines	Carbinoxamine, clemastine, dimenhydrinate, diphenhydramine, doxylamine, phenyltoloxamine	-
TYPE III Alkylamines	Brompheniramine, chlorpheniramine, dimethindene, pheniramine, tripolidine	Acrivastine
TYPE IV Piperazines	Bucizine, cyclizine, hydroxyzine, meclizine, oxatamide	Cetirizine, levocetirizine
TYPE V Piperidines	Azatadine, cyproheptadine, diphenylpyraline, ketotifen	Astemizole, desloratadine, ebastine, fexofenadine, levocabastine, loratadine, mizolastine, olopatadine, terfenadine
TYPE VI Phenothiazines	Methdilazine, promethazine	-
Others	Doxepin	Azelastine, emedastine, epinastine

Table 2: Types of H(1)-antihistamines commonly used in pediatric dermatology cases [2], [20], [21]

	Availability	Pediatric Dose (Oral Dose)
First generation H(1)-antihistamines		
Chlorphenamine (chlorpheniramine)	Syrup Tablet Intravenous	1 month-2 years: 1 mg twice daily 2-6 years: 1 mg every 4-5 hours, maximum 6 mg daily 6-12 years: 2 mg every 4-6 hours, maximum 12 mg daily 12-18 years: 4 mg every 4-6 hours, maximum 24 mg daily
Cyproheptadine	Syrup Tablet	7-14 years: 4 mg twice daily, thrice daily
Diphenhydramine	Syrup Tablet	<6 years: 6.25-12.5 mg every 4-6 hours 6-12 years: 12.5-25 mg every 4-6 hours
Hydroxyzine	Syrup Tablet	6 months-6 years: initially 5-15 mg at night, increased if needed to 50 mg daily 3-4 divided doses. 6-12 years: initially 15-25 mg at night, increased if needed to 50-100 mg daily in 3-4 divided doses. 12-18 years: initially 25 mg at night, increased if needed to 100 mg daily in 3-4 divided doses.
Promethazine hydrochloride	Syrup Tablet	2-5 years: 5 mg twice daily or 5-15 mg at night 5-10 years: 5-10 mg twice daily or 10-25 mg at night 10-18 years: 10-20 mg 2-3 times daily or 25 mg at night increased to 25 mg twice daily if needed
Second generation H(1)-antihistamines		
Acrivastine	Tablet	12-18 years: 8 mg three times a day
Cetirizine	Syrup Tablet	1-2 years: 2.5 mg daily 2-6 years: 2.5 mg, twice daily 6-12 years: 5 mg, twice daily 12-18 years: 10 mg once daily
Desloratadine	Syrup Tablet	1-6 years: 1.25 mg once daily 6-12 years: 2.5 mg once daily 12-18 years: 5 mg once daily
Ebastine	Tablet	2-5 years: 2.5 mg daily 6-12 years: 5 mg daily
Fexofenadine	Tablet	6-12 years: 30 mg twice daily 12-18 years: 120 mg once daily
Levocetirizine	Syrup Tablets	2-6 years: 1.25 mg twice daily 6-18 years: 5 mg once daily
Loratadine	Suspension Tablet	2-12 years BB <30 kg: 5 mg once daily BB >30 kg: 10 mg once daily 12-18 years: 10 mg once daily

3. Pharmacological Aspect of H(1)-Antihistamine in Pediatric

The pharmacokinetic and pharmacodynamic characteristic of drugs can generally be distinguished by age group. It determines the efficacy and safety, so that it can predict the drugs' nature that occurs in the body [10]. Although first generation H(1)-antihistamine has been used in pediatric for a long time, the pharmacological aspect is still limited [9].

In general, antihistamines are well absorbed in oral solid or liquid form, and reach the therapeutic maximum plasma concentrations between 1-4 hours after administered in children or adult [10]. The absorption of first generation H(1)-antihistamine reaches peak concentrations in plasma between 1-3 hours. In 6-16 years old children had reported that chlorpheniramine takes between 1-6 hours (average 3 hours) to achieve the maximum plasma concentration. Whereas the second generation H(1)-antihistamine in average reaches the peak plasma concentration faster; as in levocetirizine between 1-1.2 hours, and cetirizine between 0.8-2 hours, depending on age and dose given [2]. In other study reported, The pharmacokinetic second generation H(1)-antihistamine reach maximum concentration plasma between 0.8-3 hours; its metabolism ranges from minimal (fexofenadine) to longer (desloratadine and rupatadine), has terminal elimination half-life ranging from 6-27 hours [16]. Food can slow down H(1)-antihistamine absorption [1]. The pharmacokinetic is slightly affected by age, hepatic, and renal dysfunction. They are also clinically relevant to have interactions with other drugs, foods, or herbal products, even though it's rare. Pharmacodynamics of second generation H(1)-antihistamine is an onset of action ranging from 0.7-2.6 hours, has potential prolonged action ranging from 75% to 100%, and the duration of action is more than 24 hours [16].

The half life in plasma depends on drug metabolism and elimination processes in the body. The process is the same in children and adults, but it is said to occur more rapidly in several cases of children with certain antihistamines. Thus, ideal administration in some cases is once every 12 hours as opposed to once every 24 hours [10]. Although the H(1)-antihistamine has similar efficacy in the management of allergic patients, there are several chemical structures, clinical pharmacology, and toxic potential. The use of first generation H(1)-antihistamines is associated with sedation effects and impaired cognition, so that their use is shifted to second generation H(1)-antihistamine [21].

3.1 Measuring efficacy

There is no objective and adequate measurement of H(1)-antihistamine efficacy. It is subjective depending on the patient and the disease. In a previous study reported, the efficacy of H(1)-antihistamine could not be predicted solely from knowledge of in vitro potential, and the inhibition of the symptoms that present like wheal and flare was more accurate in in vivo study. However, in vivo efficacy is influenced by metabolism, excretion, lipid solubility rates, strength of binding to proteins and structural elements, their penetration and accumulation in tissue [10]. For the most

part, time to action is within one hour, with persistent effects for 24 hours. As in adult, there were no tachyphylaxis or histamine tolerance effect that induce wheal and erythema [10].

A longterm study was conducted in 15 children with mean age of 9 years old, to evaluate the onset and action duration of cetirizine and loratadine. It was found that these two antihistamines were effective in children aged 12-24 months. Long term condition, the effect of H(1)-antihistamine not immediately apparent, and the quality of life figures are seen to determine the accuracy of its efficacy [2].

4. The Use of H(1)-Antihistamines

The main use of antihistamine is to relieve allergy symptoms, which are affected by histamine release. H(1)-antihistamines are generally used to relieve itching and other symptoms due to atopic dermatitis, urticaria, allergic rhinitis, or other diseases that have high morbidity in children [1],[9]. Administration of the H(1)-antihistamine is commonly given orally, although chlorphenamine can be given intravenously, and topical preparations for the nose and eyes are also available in some H(1)-antihistamines [2]. Formulation for pediatric, liquid form is usually used, especially for age groups under 6 years old. Beside all the efficacy of the pharmacokinetic and pharmacodynamic, knowledge to improve it pleasant tasting, long lasting also important to improve patient compliance [6].

4.1 Atopic dermatitis

The use of oral H(1)-antihistamines for atopic dermatitis in children is not routinely recommended [2]. The American Academy of Dermatology (AAD) does not recommend the use of non-sedative antihistamines in the management of atopic dermatitis [22]. However, a 1-month trial with non-sedative H(1)-antihistamines can be given to children who have severe symptoms of itching or urticaria. The NICE (National Institute for Health and Care Excellence) guidelines recommend that therapy can be continued, but should be evaluated every 3 months, and can be continued if there is a positive response to therapy [3], [1]. First generation of H(1)-antihistamines can be tried for acute cases of atopic dermatitis 7-14 days in children over 6 months of age if there's sleep disturbances for the child, parents, or work. This must be considered carefully, preferably if possible, the use of sedative H(1)-antihistamines should be avoided [2], [23]. Combination H(1)-antihistamines and topical antibiotic also recommended if there is scratch because of pruritus, to prevent secondary infection [5].

4.2 Acute Urticaria and allergic reaction

H(1)-antihistamine can be administered in the emergency department for non-anaphylactic IgE-mediated hypersensitivity reactions. Administration of H(1)-antihistamine can relieve immediate symptoms and stop the progress of allergic reactions to become more severe by inactivating G-protein receptors and decreasing the release of inflammatory mediators which results in lowering the

influx of inflammatory cells [2]. H(1)-antihistamine is also said can reduce the number, size, and duration of urticarial lesions [24]. The H(1)-antihistamine that recommended by The British Society of Allergy and Clinical Immunology (BSACI) for cases of acute non-anaphylactic allergic reactions is cetirizine [2]. Second generation of H(1)-antihistamines (loratadine, cetirizine, and fexofenadine) were considered effective in controlling urticaria and had minimal side effects compared to first generation H(1)-antihistamines [10], [25], [26]. In other study reported that levocetirizine also effective in urticarial outbreaks prevention and had less effect, as demonstrated by decrease in the duration of episodes [27]. The first generation of H(1)-antihistamine may be used in conjunction with the second generation H(1)-antihistamine, if it still needed for histamine blockade. If the maximum dose of H(1)-antihistamine still has no effect, then H(2)-antihistamines such as ranitidine or cimetidine may be added [28], [26].

4.3 Anaphylaxis

Adrenaline administration in anaphylaxis cases still remains the initial therapy. H(1)-antihistamines have a slower effect than intramuscular adrenaline and it cannot block the effect of histamine when it already binds to the G-protein receptor on cells. H(1)-antihistamines do not have cardiovascular effects like adrenaline. Administration of H(1)-antihistamine following after intramuscular and intravenous fluids is recommended by the UK Resuscitation Council Guidelines of Management of Anaphylaxis [2]. Administration of chlorphenamine is part of the UK Resuscitation Council guidelines on the management of anaphylaxis after adrenaline administration [3]. Oral antihistamines can relieve mild anaphylactic reactions [1]. As for other studies, the second-line therapy after adrenaline in anaphylaxis is diphenhydramine 1-2 mg / kg every 6 hours, ranitidine 1-2 mg/kg every 12 hours, or cimetidine 4 mg/kg intravenously if needed, or other histamine H(2) receptor antagonists [28], [29].

4.4 Chronic Spontaneous Urticaria

Chronic spontaneous urticaria, which previously known as chronic idiopathic urticaria, is urticaria that appears everyday for more than 6 weeks [2], [30]. Chronic spontaneous urticaria is a long-term condition of mast cell degranulation and can be associated with various physical urticaria caused by exposure to water (aquagenic), sweat (cholinergic), sun (solar), cold, and prolonged pressure (delayed pressure urticaria) [31], [32]. The recommended therapy for chronic spontaneous urticaria is the second generation H(1)-antihistamine. If the standard doses is considered less effective, the dose can be increased four times the daily dose by increasing the frequency of drug administration [2], [3]. Recent studies suggest that administration of higher doses of levocetirizine and desloratadine is more effective in the treatment of chronic spontaneous urticaria that does not respond to standard doses [2], [33]. H(2)-antihistamines such as ranitidine and leukotriene receptor antagonists can be used as second-line therapy [2], [28].

5. Adverse Effect of Antihistamine in Pediatric Dermatologic

Antihistamines have many side effects especially in the first year of life [1]. Their use is still permitted because the pharmacovigilance system did not find any side effects that necessitated its withdrawal from the market. Many indications of antihistamine in children are based on extrapolation of the drugs effect in adults, and the dose calculations are made with little or no pharmacokinetic data according to age group difference in children [10]. The adverse effect of H(1)-antihistamines such as sedation, central nervous system disturbances (irritability or nervousness, insomnia, tremor); gastrointestinal complaints (nausea, vomit, diarrhea, constipation, anorexia); anticholinergic effect (dry mucous membranes, urinary retention, postural hypotension); cardiac arrhythmias (prolongation QT interval, ventricular arrhythmias, torsade de pointes); moreover hypersensitivity reactions [11].

The first generation H(1)-antihistamines penetrates blood brain barrier and thus have a significant effect for central nervous system giving them a sedative effect [33]. The sedating effect can be observed within 30 minutes to 1 hour and generally persist for 4-6 hours, this also may last for 24 hours or longer for some agent in some individual [11]. An excessive use can cause fatigue, somnolence, nausea, vomit, diarrhea, mydriasis, psychosis, tachycardia, hyperactivity, spasms, skin spots, and seizures [31], [34]. Respiratory system suppression, sleep apnea, blurred vision, dan dry lips can occur due to their action on cholinergic receptors [1]. There is also an occurrence of toxic encephalopathy in patients with skin syndrome (atopic dermatitis, varicella) that involve damage to skin barrier, in patients applying topical first generation H(1)-antihistamine [10]. The used in children has an impact on learning activities, that nonatopic children perform better than atopic children, and in atopic group who receive sedative antihistamines show worse performance than those who receive non sedative antihistamines [3].

Second generation H(1)-antihistamines have a larger molecular weight so that they do not easily cross the blood brain barrier, therefore have fewer side effects and sedation [31], [17], [13]. Cetirizine is one of the most second generation H(1)-antihistamine that frequently has a sedating effect, especially at higher doses. It can also cause rash, headache, fatigue, drowsiness, and insomnia [31], [35]. In a study conducted by Verdu E. et al, it was found that the severity overdose cases of second generation H(1)-antihistamine was low, because only 9% of children had symptoms, and the rest showed relatively no or mild symptoms [12]. Although its rare, it can also cause nausea, vomit, headache, dry lips, anticholinergic effects, slight sedation, extra pyramidal reactions, palpitations, and tachycardia [18], [34].

First generation H(1)-antihistamine (terfenadine, astemizole) have been associated with cardiac disorders such as torsade de pointes, which were reported while discontinuation. Meanwhile, second generation H(1)-antihistamines (cetirizine, loratadine, and fexofenadine) do not have cardiac

side effects [3]. Potential lethal can occur in overdose of first generation H(1)-antihistamines, due to cessation of the cardiorespiratory system and death because of intoxication. However, data on overdoses on second generation H(1)-antihistamines are scanty. It was reported that two children who overdosed on cetirizine experienced agitation accompanied by vomit and drowsiness [3]. And also, because of the second generation mainly used as primary treatment choice for urticaria, many physicians rarely see fact that skin eruption with pruritus can be caused and/or exacerbated after antihistamines administration [35].

6. Conclusion

Antihistamines are drugs that are commonly used in cases of pediatric dermatology, such as atopic dermatitis, acute and chronic urticaria, and allergic reactions. It can be categorized into first and second generation H(1)-antihistamines; the pharmacological effects are the same, but the second generation has fewer side effects. The half-life of the H(1)-antihistamine drug in plasma is said to occur more rapidly in several cases of children with certain antihistamines, hence the ideal drug administration time in some cases is once every 12 hours. The first generation of H(1)-antihistamines have a sedative effect because it can penetrate the blood brain barrier and thus have a significant effect in the central nervous system. That sedative effect may cause decreased children's learning performance at school. It is also said that the first generation of H(1)-antihistamine has anticholinergic effects and arrhythmia in several cases. Therefore, the second generation of H(1)-antihistamines are the drug of choice for allergy cases because of their high selectivity to H1 receptors, high efficacy, and minimal side effects. Adverse reaction in children reported against multiple antihistamine administered, although antihistamine is an important drug for use, should not forget that antihistamine also can cause severe reaction and not completely safe drugs.

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