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Navigating allergies safely: tailored solutions in special circumstances – a comprehensive review of antihistamines

Bezpieczne nawigowanie w leczeniu alergii: personalizowane rozwiązania w szczególnych okolicznościach – kompleksowy przegląd leków antyhistaminowych

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Abstract

Personalised medicine is critical in managing allergic diseases, with the variety of second-generation antihistamines necessitating tailored approaches to individual patient needs. This encompasses considerations of age, pregnancy, breastfeeding, hepatic and renal failure, drug interactions, and aging. This paper synthesises current research and guidelines on the use of antihistamines across diverse clinical scenarios, paying special attention to paediatric allergy treatment, including safety profiles of first- and second-generation antihistamines, their use during pregnancy, breastfeeding, and interactions with other drugs, as well as considerations for elderly patients. Second-generation antihistamines are preferred for allergy treatment due to their safety, minimal adverse effects, and efficacy, with a strong recommendation against the use of first-generation antihistamines due to their potential to induce severe adverse reactions. Cetirizine, levocetirizine, and desloratadine are favoured in infants; whereas loratadine, rupatadine, and bilastine are recommended for preschoolers and older children. The safety of selected second-generation antihistamines during pregnancy (notably cetirizine, levocetirizine, desloratadine) and breastfeeding (notably loratadine, desloratadine, fexofenadine), in patients with renal failure and elderly patients (bilastine, desloratadine, fexofenadine), and patients with hepatic failure (bilastine, fexofenadine) is highlighted. The choice of second-generation antihistamines should be based on the patients' individual needs and conditions to achieve optimal therapeutic outcomes and ensure safety, emphasising the importance of drug selection in varying clinical contexts.

Keywords: antihistamine, children, allergy, pregnancy, treatment

Streszczenie

Medycyna spersonalizowana jest kluczowym elementem postępowania terapeutycznego w wielu schorzeniach, w tym w chorobach alergicznych. Dysponujemy dziś wieloma lekami antyhistaminowymi II generacji i konieczne jest ich dostosowanie do indywidualnych potrzeb pacjentów, z uwzględnieniem różnych sytuacji medycznych, takich jak wiek dziecięcy lub podeszły, ciąża, laktacja, niewydolność wątroby i nerek oraz interakcje lekowe. W artykule dokonano przeglądu badań i aktualnych wytycznych dotyczących stosowania leków antyhistaminowych w leczeniu alergii w różnych sytuacjach klinicznych. Omówiono zarówno specyfikę leczenia alergii u dzieci, w tym problemy związane z bezpieczeństwem leków antyhistaminowych I i II generacji, jak i stosowanie tych leków podczas ciąży i laktacji, u osób przyjmujących inne leki i narażonych na interakcje lekowe oraz u osób starszych. Leki antyhistaminowe II generacji są preferowaną opcją w leczeniu alergii ze względu na bezpieczny profil, ograniczone działania niepożądane i skuteczność. Podkreślono konieczność unikania leków antyhistaminowych I generacji z powodu ryzyka poważnych działań niepożądanych. Preferowanymi lekami u niemowląt są cetyryzyna, lewocetyryzyna i desloratadyna, a u dzieci w wieku przedszkolnym i starszych – loratadyna, rupatadyna i bilastyna. Wskazano również na bezpieczeństwo stosowania wybranych leków antyhistaminowych II generacji podczas ciąży (preferowane cetyryzyna, lewocetyryzyna, desloratadyna), w czasie laktacji (loratadyna, desloratadyna, feksofenadyna), w niewydolności nerek oraz u osób starszych (bilastyna, desloratadyna, feksofenadyna) i z niewydolnością wątroby (bilastyna, feksofenadyna). Wybór leku antyhistaminowego II generacji u pacjenta z alergią powinien uwzględniać jego indywidualne potrzeby, gdyż ma to zasadnicze znaczenie dla optymalnych wyników i bezpieczeństwa terapii.

Słowa kluczowe: leki antyhistaminowe, dzieci, alergia, ciąża, leczenie

INTRODUCTION

Personalised medicine has revolutionised healthcare. Its aim is to customise treatment to the specific needs and clinical symptoms of patients[1]. In the context of second-generation antihistamines (AHs), which are commonly used in the treatment of allergies and allergic reactions, it becomes crucial to consider different medical situations, such as young or advanced age, breastfeeding, pregnancy, hepatic or renal failure and drug–drug interactions.

Compliance with the principles of personalised medicine is particularly important in children, in whom age is crucial in treatment selection, while appropriate dosing of second-generation AHs, taking into account body weight and other factors, is necessary to achieve optimal efficacy and minimise potential adverse effects. Breastfeeding, pregnancy, hepatic or renal failure also require special approach to AH treatment due to the increased risk of possible adverse reactions. It should be borne in mind that hepatic and renal impairment may alter the pharmacokinetics and pharmacodynamics of these drugs, which may impact their dosage and safety.

This review paper focuses on personalised medicine for allergic diseases and the use of second-generation AHs in different clinical situations, such as children and elderly patients, breastfeeding, pregnancy, organ failure and drug–drug interactions. We present the latest scientific evidence and up-to-date guidelines to provide clinicians with a comprehensive view of the topic and to support more informed therapeutic decision-making in specific clinical situations.

THE USE OF ANTIHISTAMINES IN CHILDREN

The safety of allergy treatment in children is based the use of drugs with the highest safety profile. First-generation AHs, such as hydroxyzine and clemastine, cause sedation and impair cognitive function, and their use is associated with the risk of adverse reactions such as dry mouth, visual disturbances, hallucinations and respiratory depression. Newer, second-generation AHs, such as cetirizine, loratadine, levocetirizine, desloratadine, ebastine, fexofenadine, bilastine, rupatadine and azelastine, are safer in children as they are less likely to induce sedation and have fewer adverse effects. Tab. 1 shows the division into first- and second-generation antihistamines and their classification based on central nervous system (CNS) sedative properties (sedative, less sedative and non-sedative) (based on De Benedictis et al.)[2]. The group of sedative AHs includes two agents (diphenhydramine, promethazine) that were particularly commonly prescribed for children in the past.

The use of AHs in children encounters a number of registration problems (age restrictions) and challenges arising from the indications in the summary of product characteristics (SmPC). The fact that some paediatricians are accustomed to first-generation AHs, the so-called old antihistamines, which should be avoided due to their multiple adverse effects, is an additional barrier. These agents (e.g. dimethyndene or ketotifen) are still readily prescribed in infants and younger children (<2 years of age) as historically they did not have strict age limits for registration.

Acute urticaria (AU) and allergic rhinitis (AR) are the most common indications for AHs in the paediatric population.

Urticaria

Although food allergens and infections are the most common triggers of AU in children, the aetiology remains unknown in many cases (up to 40%)[3]. AHs are the treatment of choice in this age group[4].

The management of AU is described in the 2022 guidelines of the European Academy of Allergology, which advocate up to a fourfold increase in the dose of second-generation AHs and, if there is no clinical effect, treatment switching and further escalation (Fig. 1)[5].

Safety of first-generation antihistamines in children

Since 2007, first-generation AHs are no longer recommended in any age group due to their highly unfavourable safety profile and reported cases of child deaths[6]. In an unprecedented action, the US Food and Drug Administration (FDA) removed all cold products containing AH active substances from the US market[7–9]. Unfortunately, children

	Sedating	Less-sedating	Non-sedating
First-generations antihistamines	Diphenhydramine Dimenhydrinate Doxylamine Hydroxyzine Clemastine Promethazine	Brompheniramine Cyproheptadine Meclizine Ketotifen	Chlorpheniramine Dexchlorpheniramine Dimethindene Triprolidine
Second-generations antihistamines			Azelastine, bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, rupatadine, terfenadine

Tab. 1. Functional classification into first and second-generation antihistamines, as well as sedating, less-sedating, and non-sedating options[2]

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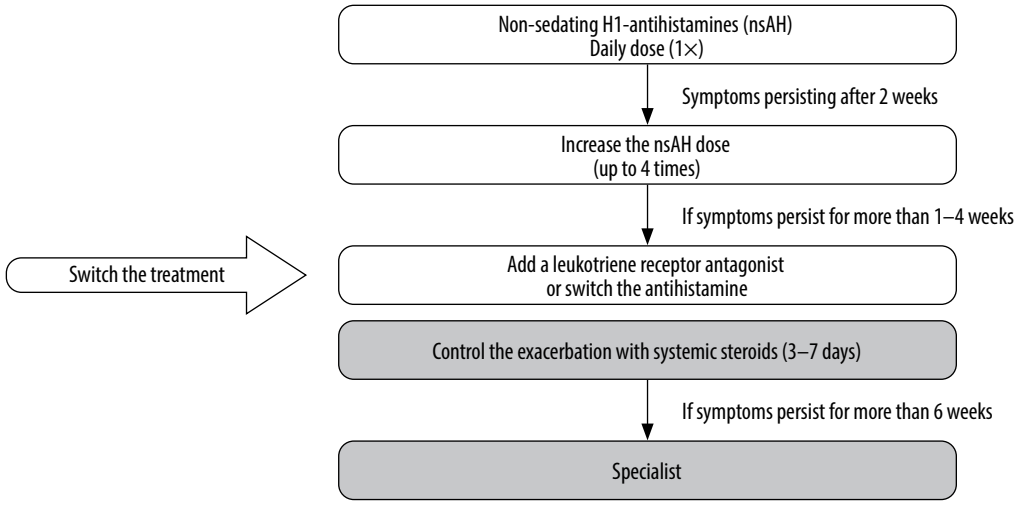

Fig. 1. A flowchart of therapeutic management in acute urticaria based on 2022 EAACI recommendations[5]

with urticaria put on first-generation AHs (e.g. clemastine, dimethindene or hydroxyzine) are still encountered in clinical practice, which is probably due to the habit of many physicians and the historically set age limits (e.g. dimethindene >1 month of age, ketotifen >7 months of age), not supported by reliable studies on the safety of use in children[10]. Well-designed safety studies in such young children are lacking. The dosage of AHs in patients <2 years of age is not entirely clear and is based on old habits rather than SmPC data; in the light of reports by the European Medicines Agency (EMA) and the European Academy of Allergy and Clinical Immunology (EAACI), such treatment should not be recommended[11,12]. Many of these agents cause serious adverse effects such as sedation, drowsiness and cognitive deficits, hallucinations and even respiratory depression, and should therefore not be used to treat allergic diseases in children <2 years of age[13].

Only second-generation AHs are currently recommended for the treatment of allergies in young children (2–6 years): cetirizine, levocetirizine, loratadine, desloratadine, rupatadine and bilastine (see Tab. 2 for the recommended age for each product).

Antihistamine	Recommended age
Cetirizine	≥6 months
Levocetirizine	≥6 months
Desloratadine	≥6 months*
Loratadine	≥2 years
Rupatadine	≥2 years
Bilastine	≥6 years
Ebastine	≥12 years
Fexofenadine	≥12 years
* Approved for children from 1 year of age in Poland.	

Tab. 2. Approved age recommendations for second-generation antihistamines (according to summary of product characteristics)

It is worth noting at this point that although cetirizine and levocetirizine are registered for the treatment of AR, the SmPC suggests that they can be used in children with food allergy, anaphylactic reaction and urticaria as early as at >6 months of age. These medications have also been reimbursed for off-label indications, and can be prescribed at a discount. This also applies to **desloratadine**, which has broader registration indications and very wide dosing options depending on the child's age (5 mg/day for adolescents >12 years and adults, 2.5 mg/day for children aged 6–11 years and 1.25 mg/day in the form of a syrup for children aged 1–5 years).

It should be added in this context that AHs, despite their widespread use, are not recommended by EAACI for the prevention or treatment of anaphylactic reaction[14].

Atopic dermatitis

Special attention should be paid to the relatively common practice of prescribing AHs in atopic dermatitis (AD), which stems from an unfounded belief that it is excessive histamine release that causes skin lesions in AD. According to the contemporary view, pruritus in AD is due to increased inflammation associated with increased secretion of Th2-type interleukins (IL-4, IL-5, IL-13 and IL-31) and Th17-type interleukins (Th17, Th22), as well as disruption of the skin barrier and release of alarmin cytokines (TSLP, IL-33, IL-25), i.e. mediators other than histamine[15,16]. Therefore, the view that drugs in this group may have contributed to the rapid resolution of skin lesions and persistent pruritus is erroneous[15]. In practice, it is common to see infants treated for AD with first-generation AHs (ketotifen or dimethindene). It should be stressed that this is a completely erroneous approach not supported by knowledge of the pathogenetic mechanisms underlying this disease[15–17]. Pruritus results from inflammation in the skin, which is most effectively treated with topical agents

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(steroids, calcineurin inhibitors)[16]. Although the latest UK 2023 recommendations suggest the possibility of **a 1-month trial with a non-sedating AH** (e.g. **cetirizine, levocetirizine or desloratadine**), it is important to bear in mind that the treatment should be discontinued if there is no apparent effect over and above the current topical treatment that is recommended as the basis of management[18].
At this point, it is important to point to impaired CNS and cognitive function associated with the use of sedative first-generation AHs.

Sedative effects of antihistamines on the central nervous system in children

Misattributing the role similar to "small benzodiazepines" to sedative AHs is a common misunderstanding in terms of their sedative effects[17]. They are thought to have sedative, hypnotic and anxiolytic action. Hydroxyzine is particularly favoured in this context. However, the observed sedation is due to a completely different mechanism. Firstly, after passing the blood–brain barrier (BBB), the drug interferes with the rapid eye movement (REM) activity of the brain, reducing it by up to 25%, and thus affecting REM sleep phases[12,19]. Secondly, delayed onset of sleep, resulting in concentration difficulties and significantly disrupted cognitive abilities during waking hours due to insufficient sleep duration after taking the drug, is an additional burdening aspect[12,20]. This effect is not observed with non-sedating second-generation AHs. Adverse effects of BBB-crossing AHs, which compromise kindergarten or school performance in children or work performance/driving abilities in adults, are shown in Tab. 3.

• Drowsiness
• Blurred vision
• Dizziness
• Headaches
• Fatigue
• Double vision
• Tinnitus
• Drops in blood pressure
• Cardiac rhythm disturbances – particularly in patients with pre-existing conditions regardless of pharmacotherapy

Tab. 3. Adverse effects of BBB-crossing antihistamines[31]

ALLERGIC RHINITIS

In the context of AR, systemic (oral) AHs may be used the same as intranasal AHs (azelastine and olopatadine), intranasal steroids and nasal steroids combined with topical (intranasal) AHs[21]. However, clinical practice indicates that most patients prefer the oral form of the drug. Oral non-sedating second-generation AHs, in particular **levocetirizine, loratadine, desloratadine, rupatadine, bilastine** and **fexofenadine**, are recommended for children and adolescents (i.e. older children, usually not infants) with AR.
Combinations of nasal AHs with a steroid are an interesting new option. Two such combined preparations are available on the market: mometasone/olopatadine and fluticasone/azelastine. Such a combination shows a synergistic effect in controlling AR symptoms compared with each of these drugs used alone[22].

Time of day and the most optimal clinical effect of antihistamine

It is worth noting that the pharmacokinetics and half-life of these drugs (between 6 hours for cetirizine and up to 17 hours for fexofenadine) suggest that they are **best taken in the morning** for the most optimal clinical effect[23]. Unfortunately, it is not uncommon to see patients taking these drugs in the evening for fear of adverse effects (drowsiness). This is inappropriate and completely unjustified as all oral AHs reach their maximum plasma levels after only 1–2 hours, i.e. at the time when patients expect to enjoy the highest mental and physical activity, and at the same time they are most in need for protection from allergens[24].

PREGNANCY AND BREASTFEEDING

The use of oral medications during pregnancy may carry a risk for the foetus. Due to the significant prevalence of allergies in European countries, AHs rank as the fourth most commonly prescribed oral medications during pregnancy[25]. It is therefore necessary for every pregnant woman with a allergy to carefully consider the safety and efficacy of these drugs for both herself and the foetus.
Research on the safety of AHs during pregnancy is limited, mainly due to the ethical and practical challenges associated with enrolling pregnant women in clinical trials. However, databases on women who have used AHs during pregnancy allows for risk/benefit assessment in this group of patients. An analysis of a large number of cases and animal studies found that cetirizine, levocetirizine and loratadine do not represent a major teratogenic risk[26,27]; as a result, these three agents have been classified as pregnancy safety category B, allowing for their use in expectant mothers (Tab. 4). It is also assumed that the other agents in this group, which have a pregnancy category C (can be used when the benefits outweigh the risks), are less safe.

Antihistamines during breastfeeding

The use of AHs should be approached with caution during breastfeeding to ensure the safety of both mother and her infant. A growing research on the safety of AHs in breastfeeding women can be found in the literature. According to EAACI and GA²LEN recommendations, second-generation AHs such as **loratadine and desloratadine** are preferred during breastfeeding due to limited penetration into breast milk and negligible sedative effects[28]. **Terfenadine and fexofenadine** have been detected in breast milk, but

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Category A	X
Category B	Cetirizine, levocetirizine, loratadine
Category C	Desloratadine, fexofenadine, bilastine, rupatadine, ebastine, azelastine, olopatadine
Category X	All first-generation (sedating) antihistamines (hydroxyzine, clemastine, and others)

Tab. 4. The safety of antihistamines in pregnancy according to FDA classification. Categories A and B – highest safety profile. Category X – absolutely contraindicated (according to FDA.gov)

their presence has not been linked with adverse effects on infants, indicating their relative safety during the breastfeeding period[29,30]. Decisions on the use of AHs in breastfeeding mothers should be based on the individual medical assessment, taking into account maternal health status, potential risks to the infant and available treatment options.

DRUG–DRUG INTERACTIONS

With regard to AHs, pharmacokinetic interactions that occur at the metabolic stage involving cytochrome P450 (CYP 450) isoenzymes are of greatest importance. Therefore, the choice of AH should be guided by the potential risk of adverse interactions with other drugs taken by the patient[31]. The risk increases when the administered antihistamine is metabolised with the involvement of cytochrome P450. Therefore, it is advisable to select medications that are not metabolised by CYP 450 to prevent drug interactions and their clinical consequences, as well as to avoid the need for treatment modification. One could even venture to say that the risk of interaction in polytherapy is the **most important** AH selection criterion. **Allergic diseases and asthma are among the most common chronic conditions** and are associated with a **particularly high risk of polytherapy**[32]. The available pharmacoepidemiological studies have shown that the risk of excessive polytherapy increases 4.5-fold in patients with allergic diseases[32]. Similarly, other observations have shown that the risk of polytherapy was particularly pronounced in cardiovascular diseases, pain management, and allergic conditions[33]. There is a strong correlation between an increased risk of polytherapy and the multi-specialist treatment model. The more treating physicians involved, the greater the risk of polypragmasy, which is most commonly associated with a lack of coordination among prescribed medications, particularly a lack of coordination in pharmacotherapy within the framework of primary care physician oversight of the patient's care. It is worth noting that there is a varying risk of interactions in the antihistamine class, which is associated with the characteristics of individual AHs.

Interactions for loratadine

Food delays the absorption of this drug. Adverse effects may include dry mouth, hair loss, liver dysfunction, allergic reactions, supraventricular cardiac arrhythmias, and sedation, which may be more pronounced than with desloratadine. The drug is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6, resulting in a real risk of pharmacokinetic interactions with CYP3A4 inhibitors (azole antifungals, erythromycin, clarithromycin) and grapefruit juice. They may increase the risk of cardiac arrhythmias[34]. There is also a risk of interactions with CYP2D6 inhibitors, which is of particular importance in individuals characterised by slow CYP2D6 metabolism, who account for 6–14% of the Polish population[24].

Interactions for desloratadine

Drug levels may increase up to 2.5-fold in patients with hepatic or renal insufficiency (Tab. 5). The half-life and protein binding capacity are of practical importance for both quantitative and qualitative assessments (the severity of adverse reactions) of drug interactions. The following adverse reactions may occur: headache, dry mouth, dizziness and (very rarely) sedation. The medication does not exacerbate the adverse effects of ethyl alcohol on the CNS. To date, no interactions with other co-administered drugs have been identified and the risk of pharmacokinetic interactions is described as negligible[34]. This is of particular importance in patients on polypharmacotherapy, when there is an increased risk of adverse drug interactions.

Interactions for cetirizine

Cetirizine is an active metabolite of hydroxyzine, formed by an oxidation reaction. Although cetirizine penetrates the CNS to a lesser extent than hydroxyzine and is recognized as a second-generation antihistamine, **its sedative effect on the CNS is significantly greater compared to other second-generation antihistamines**[24]. Theophylline slightly decreases the clearance of cetirizine. Caution should be exercised during concomitant use of CNS depressants. There were no clinically significant interactions with erythromycin, pseudoephedrine, azithromycin, ketoconazole, cimetidine, diazepam or glipizide[34]. Ritonavir increases exposure to cetirizine. Although no clinically significant interactions with alcohol have been reported, it should be avoided during cetirizine use due to its potential to exacerbate CNS adverse reactions.

Interactions of levocetirizine

As levocetirizine (cetirizine R-enantiomer) has twice the affinity for the H_1 receptor compared to cetirizine, it can be used at a dose of 5 mg, which in turn reduces the incidence of adverse reactions such as sedation and anticholinergic symptoms[31]. Both cetirizine and levocetirizine may exacerbate the CNS depressant effects of other co-administered drugs (sedatives, hypnotics, antidepressants with

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Antihistamine	Elimination	Dosing implications in patients with liver and/or kidney dysfunction
Cetirizine	Cetirizine is predominantly excreted in urine (approximately 70% of the dose, mostly unchanged) and to a lesser extent in faeces (around 10%)	Mild renal dysfunction does not significantly affect the clearance of cetirizine. In individuals with moderate renal impairment or undergoing hemodialysis, the half-life is prolonged 3-fold, and clearance decreases by 70%. Chronic liver diseases are associated with a 50% increase in half-life and a 40% decrease in clearance
Levocetirizine	Levocetirizine and its metabolites are excreted in urine through both glomerular filtration and tubular secretion, while approximately 13% is excreted via faeces	Dosage adjustment is not necessary in patients with liver dysfunction. Adults with creatinine clearance of 30–49 mL/min and 10–30 mL/min are recommended a dose of 5 mg every 2 days and 5 mg every 3 days, respectively. Detailed data on patients with renal impairment are lacking; therefore, the dose should be individually adjusted, considering the patient's renal clearance and body weight
Loratadine	80% of the dose is excreted as metabolites in the urine and faeces within 10 days post-administration. The half-life of loratadine is 8.4 hours (3 to 20 hours), while that of desloratadine is 27 hours (9 to 92 hours). In elderly patients, the half-life of loratadine is 18.2 hours, and for its main metabolite, it is 17.5 hours. In patients with impaired liver function, the half-life is 24 hours (37 hours for the main metabolite)	Dosage modification is not necessary in patients with renal impairment and elderly patients. However, the drug's action is prolonged in cases of renal or hepatic insufficiency and in elderly patients, which should be considered in the dosing regimen
Desloratadine	Excreted in similar proportions in both urine and faeces	Caution should be exercised in cases of liver or kidney insufficiency
Fexofenadine	Elimination primarily in bile, with up to 10% of the substance excreted unchanged in urine	Dosage adjustment is not needed in patients with liver or kidney insufficiency
Rupatadine	Excreted in both urine and faeces	Due to the lack of clinical experience in patients with renal or hepatic impairment, caution should be exercised in these patients
Bilastine	95% of the single dose is excreted unchanged, with approximately 28% in urine and about 66% in faeces	Dosage modification is not needed in elderly individuals or those with renal or hepatic dysfunction
Ebastine	Approximately 66% of the administered dose is excreted in urine, primarily in the form of metabolites. There are no significant changes in the pharmacokinetic profile of cerebastine (metabolite of ebastine) in elderly individuals	The half-life of cerebastine is prolonged to 23–26 hours in patients with renal insufficiency and to approximately 27 hours in cases of hepatic insufficiency. There is no need for dosage adjustment in individuals with renal impairment or mild to moderate hepatic dysfunction

Tab. 5. The use of antihistamines in patients with liver and/or kidney dysfunction

sedative effects, antipsychotics, and opioid analgesics). Both drugs may impair ability to drive and perform complex activities[34].

Interactions for fexofenadine

Although fexofenadine is a metabolite of terfenadine (AH), it lacks the adverse effects characteristic of the parent drug. Fexofenadine should not be co-administered with strong CYP3A4 inhibitors and antacids, which may reduce the gastrointestinal absorption of the drug[31,34].

Interactions for rupatadine

Rupatadine is an AH that simultaneously inhibits platelet-activating factor (PAF). It has no sedative effect and does not impact the length of the QTc interval. Due to the lack of clinical trials in patients with renal or hepatic impairment, caution should be exercised in this population[31]. Since the drug is metabolised via CYP3A4, caution should be exercised when administering it to patients put on CYP3A4 inhibitors (such as erythromycin, fluconazole, diltiazem) and statins metabolised by this isoenzyme (lovastatin, simvastatin, atorvastatin). Grapefruit juice, which enhances the systemic exposure to the drug 3.5-fold, should not be consumed during rupatadine treatment. Dose adjustment of agents sensitive to CYP3A4 (atorvastatin, simvastatin, lovastatin) and medications with a narrow therapeutic index that are substrates for the CYP3A4 isoenzyme (e.g. cyclosporine, tacrolimus, sirolimus, everolimus, cisapride) may be necessary, as rupatadine may increase plasma levels of these drugs. Caution should be exercised when co-administering rupatadine with other metabolised drugs with a narrow therapeutic index. Rupatadine 20 mg co-administered with alcohol produced more psychomotor impairment, whereas a dose of 10 mg was associated with disturbances of similar severity to that observed with alcohol alone[31,34].

Interactions for bilastine

Bilastine has high affinity for the H_1 receptor. It has no effect on muscarinic receptors and no sedative effect. **Food affects the gastrointestinal absorption of the drug**, hence the recommendation to take it before a meal, or alternatively, two hours after a meal[10]. As bilastine does not undergo hepatic metabolism, it does not interact adversely with other concomitantly used drugs. The drug is eliminated with faeces in an unchanged form, but a small portion of it is excreted in urine. There is no need for dose modification in patients with hepatic or renal insufficiency. Bilastine

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can be safely used by drivers. It does not affect the length of the QTc interval, hence it can be safely used in patients with cardiovascular diseases. Concomitant use of drugs affecting the activity of P-glycoprotein or organic anion transporting polypeptides, or which are their substrates, may affect bilastine concentrations. Simultaneous administration of ketoconazole or erythromycin increases the area under the curve (AUC) and maximum serum concentration (C_{max}) of bilastine, while diltiazem increases its serum levels. Ritonavir and rifampicin may decrease plasma levels of bilastine. Bilastine does not potentiate the CNS depressant effects induced by lorazepam or alcohol-induced disturbances[31].

Interactions for ebastine

Co-administration of ebastine with CYP3A4 inhibitors is associated with an increase in its serum levels. When ebastine was used concomitantly with CYP3A4 inhibitors, increased plasma levels of ebastine and, to a lesser extent, of carebastine were observed, with no clinically significant pharmacodynamic consequences. On the other hand, inducers of CYP3A4, such as rifampicin, carbamazepine, St. John's Wort extracts, barbiturates and dexamethasone, decrease serum ebastine and compromise its antihistamine action.

ELDERLY PATIENTS

In the elderly population, due to possible AH-induced adverse reactions and age-related changes in pharmacokinetics, three issues are particularly relevant from a practical standpoint:

1. sedation or its severity due to AHs in polypharmacotherapy;
2. cardiovascular safety of AHs;
3. impact on road safety due to possible drug interactions at this age and further impairment of psychophysical performance of drivers[33].

Antihistamines and sedation

AH-induced sedation may contribute to falls and injuries, often resulting from frailty syndrome. **Bilastine, desloratadine** and **fexofenadine** are recommended in elderly patients requiring AH treatment[31].

Cardiovascular safety of antihistamines

Second-generation AHs are characterised by an optimal cardiovascular risk profile[24]. This is due to their receptor selectivity and the centralised assessment of electrocardiograms (ECGs) by expert cardiologists during clinical trials of new drugs in all phases of research. Astemizole was the drug that first drew attention to the effects of AH on cardiac function. Only later clinical trials in humans and experiments on animals revealed that astemizole and terfenadine strongly inhibit potassium channels in cardiac muscle cells, leading to delayed ventricular repolarisation, clinically associated with prolongation of the QTc interval. This directly leads to a significant increase in the risk of life-threatening ventricular arrhythmias, clinically described as the risk of torsadogenicity associated with these antihistamines[33]. Therefore, these drugs have been withdrawn from the pharmaceutical market due to their relatively high risk of cardiovascular adverse effects. The risk of torsadogenicity does not apply to AHs other than astemizole and terfenadine, and is therefore not a characteristic of this class, and since this discovery, clinical trials on all AHs have assessed their effect on QTc interval.

The new guidelines on the treatment of chronic urticaria have changed the perspective on the potential and actual safety of AHs. They postulate increasing the standard dose of AH to a quadruple dose, which may prolong the QTc interval, but this risk should be assessed individually.

Studies have shown that **bilastine** has relatively **the best cardiovascular safety profile**[31]. When used at doses of 20–100 mg (five times the registered dose), it had no effect on either ECG morphology or QTc interval duration[31]. It was also found to have no effect on ECG morphology or QTc duration in any clinical trial, which is particularly important in patients with risk factors for ventricular arrhythmias.

Antihistamines and driving performance

AHs, first-generation AHs that cross the blood-brain barrier in particular, may significantly impair psychophysical performance, which is particularly relevant for those driving motor vehicles[33]. Adverse effects of these drugs that increase the risk of impaired driving performance are listed in Tab. 6. It is worth noting that due to their pharmacokinetic parameters, AHs **may have greater impact on driving ability than alcohol**[35].

Bilastine, desloratadine or fexofenadine are recommended for drivers and aircraft pilots requiring AH treatment due to inhalant allergy.

- Prolonged reaction time, typically by 3–5 seconds, depending on patient's residual characteristics, comorbidities, and co-administered medications
- Impaired distance estimation – risk of rear-end collisions or striking a static obstacle
- Blurred vision
- Worsening of vision in darkness – anticholinergic effect
- Falling asleep while driving
- Uncontrolled lane changing – potential for driving against oncoming traffic, incorrect taking turns
- Sudden disruption of trajectory – anticholinergic effect, inducing dizziness, hypotensive effect
- Inadequate response to sudden situations and hazards in traffic, including improper reactions to priority vehicles – tinnitus, visual field disturbances, blurred vision, double vision, prolonged reaction time due to sedation

Tab. 6. Adverse effects of first-generation AHs with central antihistamine activity and their consequences leading to impaired ability to safely operate vehicles[31]

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Situation	Recommended	Not recommended
Infants Young children (<2 years old)	Cetirizine Levocetirizine Desloratadine	Dimethindene Ketotifen Clemastine
Preschool children (2–6 years old)	As above + Loratadine Rupatadine	Promethazine Diphenhydramine
School-age children	As above + Fexofenadine Bilastine	As above
Pregnancy	Cetirizine Levocetirizine Loratadine	Desloratadine Fexofenadine Bilastine Rupatadine Ebastine Azelastine Olopatadine All first-generation AHs
Breastfeeding	Loratadine Desloratadine Fexofenadine	All other AHs
Renal failure	Bilastine Desloratadine Fexofenadine	All other AHs
Liver failure	Bilastine Fexofenadine	Cetirizine Loratadine Ebastine Levocetirizine Desloratadine Rupatadine (need for dose adjustment in liver impairment)
Advanced age	Bilastine Desloratadine Fexofenadine	All other AHs

Tab. 7. Recommendations and contraindications for the use of antihistamines in different age groups and clinical circumstances

CONCLUSIONS

The 21st century is the time of personalised medicine also in the treatment of allergies and the use of AHs. Today, instead of simply recommending "some antihistamine" we rather strive to tailor the treatment to the specific clinical situation, the age of the patient (infant, preschool child, adolescent), comorbidities (internal organ failure, multimorbidity), and even perinatal circumstances in allergic patients (pregnancy, breastfeeding) (Tab. 7)[33].

Conflict of interest

WF received remuneration for delivering lectures from the following companies: Polpharma, Glenmark, Adamed, and Berlin Chemie.

Author contribution

Original concept of study: WF. Collection, recording and/or compilation of data: WF. Analysis and interpretation of data: WF, JW. Writing of manuscript: WF, JW. Critical review of manuscript: WF, JW. Final approval of manuscript: WF, JW.

References

1. Jameson JL, Longo DL: Precision medicine – personalized, problematic, and promising. N Engl J Med 2015; 372: 2229–2234.
2. de Benedictis FM, de Benedictis D, Canonica GW: New oral H1 antihistamines in children: facts and unmeet needs. Allergy 2008; 63: 1395–1404.
3. Kim EJ, Zhang Z, Hlobik M et al.: Urticaria in infants: a single-institution retrospective study. Pediatr Dermatol 2024; 41: 260–262.
4. Jamjanya S, Danpanichkul P, Ongsupankul S et al.: Evaluation of pharmacological treatments for acute urticaria: a systematic review and meta-analysis. J Allergy Clin Immunol Pract 2024: S2213-2198(24)00074-6.
5. Zuberbier T, Abdul Latiff AH, Abuzakouk M et al.: The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2022; 77: 734–766.
6. Dart RC, Paul IM, Bond GR et al.: Pediatric fatalities associated with over the counter (nonprescription) cough and cold medications. Ann Emerg Med 2009; 53: 411–417.
7. Lazarus SG, Lanski SL, Smith AS et al.: Cold preparation use in young children after FDA warnings: do concerns still exist? Clin Pediatr (Phila) 2013; 52: 534–539.
8. Yehya A, Numan M, Matalqah L: No time for lullabies: tracing down pharmacological effects & uses of H1-antihistamines in children younger than 6 years. Glob Pediatr Health 2021; 8: 2333794X21992170.
9. Sharfstein JM, North M, Serwint JR: Over the counter but no longer under the radar – pediatric cough and cold medications. N Engl J Med 2007; 357: 2321–2324.
10. Parisi GF, Licari A, Papale M et al.: Antihistamines: ABC for the pediatricians. Pediatr Allergy Immunol 2020; 31 Suppl 24: 34–36.
11. European Medicines Agency: PRAC recommends new measures to minimise known heart risks of hydroxyzine-containing medicines. European Medicines Agency, 2015. EMA/85678/2015.
12. Church MK, Maurer M, Simons FER et al.: Risk of first-generation H_1-antihistamines: a GA²LEN position paper. Allergy 2010; 65: 459–466.
13. Pampura AN, Papadopoulos NG, Spičák V et al.: Evidence for clinical safety, efficacy, and parent and physician perceptions of levocetirizine for the treatment of children with allergic disease. Int Arch Allergy Immunol 2011; 155: 367–378.
14. Muraro A, Worm M, Alviani C et al.; European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group: EAACI guidelines: anaphylaxis (2021 update). Allergy 2022; 77: 357–377.
15. Osinka K, Dumycz K, Kwiek B et al.: Novel therapeutic approaches to atopic dermatitis. Arch Immunol Ther Exp (Warsz) 2018; 66: 171–181.
16. Wollenberg A, Kinberger M, Arents B et al.: First update of the living European guideline (EuroGuiDerm) on atopic eczema. J Eur Acad Dermatol Venereol 2023; 37: e1283–e1287.
17. He A, Feldman SR, Fleischer AB Jr: An assessment of the use of antihistamines in the management of atopic dermatitis. J Am Acad Dermatol 2018; 79: 92–96.
18. Matthews SJ, Housam N, Lawton S et al.: Atopic eczema in under 12s: diagnosis and management-summary of updated NICE guidance. BMJ 2023; 382: 1538.
19. Boyle J, Eriksson M, Stanley N et al.: Allergy medication in Japanese volunteers: treatment effect of single doses on nocturnal sleep architecture and next day residual effects. Curr Med Res Opin 2006; 22: 1343–1351.
20. Church MK: Allergy, histamine and antihistamines. Handb Exp Pharmacol 2017; 241: 321–331.
21. Fokkens WJ, Lund VJ, Hopkins C et al.: European position paper on rhinosinusitis and nasal polyps 2020. Rhinology 2020; 58 (Suppl S29): 1–464.

22. Gross GN, Berman G, Amar NJ et al.: Efficacy and safety of olopatadine-mometasone combination nasal spray for the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2019; 122: 630–638.e3.

23. Delgado J, Dávila IJ, Domínguez-Ortega J; Severe Asthma Group (SEAIC): Clinical recommendations for the management of biological treatments in severe asthma patients: a consensus statement. J Investig Allergol Clin Immunol 2021; 31: 36–43.

24. Li L, Liu R, Peng C et al.: Pharmacogenomics for the efficacy and side effects of antihistamines. Exp Dermatol 2022; 31: 993–1004.

25. Dávila I, del Cuvillo A, Mullol J et al.: Use of second generation H_1 antihistamines in special situations. J Investig Allergol Clin Immunol 2013; 23 Suppl 1: 1–16.

26. Etwel F, Djokanovic N, Moretti ME et al.: The fetal safety of cetirizine: an observational cohort study and meta-analysis. J Obstet Gynaecol 2014; 34: 392–399.

27. Seto A, Einarson T, Koren G: Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. Am J Perinatol 1997; 14: 119–124.

28. Zuberbier T, Aberer W, Asero R et al.; endorsed by the following societies: AAAAI, AAD, AAIITO, ACAAI, AEDV, APAAACI, ASBAI, ASCIA, BAD, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGAKI, DSA, DST, EAACI, EIAS, EDF, EMBRN, ESCD, GA²LEN, IAACI, IADVL, JDA, NVvA, MSAI, ÖGDV, PSA, RAACI, SBD, SFD, SGAI, SGDV, SIAAIC, SIDeMaST, SPDV, TSD, UNBB, UNEV and WAO: The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018; 73: 1393–1414.

29. Van de Perre P, Molès JP, Nagot N et al.: Revisiting Koch's postulate to determine the plausibility of viral transmission by human milk. Pediatr Allergy Immunol 2021; 32: 835–842.

30. Gade EJ, Tidemandsen C, Hansen AV et al.: Challenges in the successful management of asthma during conception, pregnancy and delivery. Breathe (Sheff) 2022; 18: 220013.

31. Woroń J: Wybór leku przeciwhistaminowego w farmakoterapii chorób alergicznych. O czym warto pamiętać stosując bilastynę? Terapia 2023; 31 (1): 40–45.

32. Shakhova NV, Kashinskaya TS, Kamaltynova EM: Prevalence of bronchial asthma and allergic diseases among children. Allergology and Immunology in Pediatrics 2022; 69: 5–12.

33. Kuna P, Jurkiewicz D, Czarnecka-Operacz MM et al.: The role and choice criteria of antihistamines in allergy management – expert opinion. Alergologia Polska – Polish Journal of Allergology 2017; 4: 7–19.

34. Pawłowska I, Kuźbicka K, Krzyżaniak N et al.: Interactions between selected over-the-counter drugs and food: clinical relevance and prevention. Int J Food Sci Nutr 2022; 73: 1005–1018.

35. Verster JC, Mets MA: Psychoactive medication and traffic safety. Int J Environ Res Public Health 2009; 6: 1041–1054.