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Clinical Pharmacology Review for Primary Health Care Providers: I. Antihistamines

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Primary health care providers play a critical role in maintaining public health, and the appropriate use of pharmaceutical products is one of the major parts of their practice. This series of articles, entitled 'Clinical Pharmacology Review for Primary Health Care Providers,' is intended to help primary health care providers select more appropriate prescriptions for frequently used drugs based on up-to-date information. We expect that this effort will contribute to improvements in public health and diminish unnecessary drug use.

Introduction

Antihistamines include some of the most frequently prescribed drugs in the primary health care environment for the symptomatic relief of allergic diseases, the common cold, urticaria, and insomnia.[1-5] The importance of antihistamines has been emphasized as the prevalence of target diseases increases.[6,7] However, the appropriate use, clinical effectiveness, and target populations for prescription of antihistamines are still a matter of debate.

Antihistamines antagonize the actions of histamine, which is released from mast cells in inflammatory processes including type I hypersensitivity allergic reactions. However, antihistamines do not antagonize histamine binding on all types of histamine receptors. Antihistamines are H_1-receptor antagonists.[8] In addition, many studies report that antihistamines are inverse agonists to corresponding receptors rather than simply antagonists.[9] H_2-receptor antagonists (H_2-blockers) constitute another widely used class of drugs that mainly block histamine action in the stomach, resulting in decreased gastric acid secretion. H_3- and H_4-receptor are not yet clinically available, although many candidates are currently in human trials.[10] For this reason, the term 'H_1 antihistamine' is used for clear categorization.[8,9] Antihistamines should also be distinguished from 'mast cell stabilizers' such as cromolyn and nedocromil because their activity is limited to the inhibition of released histamine from mast cells. Several antihistamines exhibit antiallergic and anti-inflammatory properties that are independent of their action on the H1 receptor.[8]

Generations and Classes

Many primary health care providers are well-informed about the different 'generations' of antihistamines but not about the different 'classes' characterized according to chemical structure.[1] This discrepancy seems reasonable because 'inter-generation' differences are more prominent than 'inter-class' differences. In other words, understanding 'inter-generation' differences is essential to primary health care providers in a way understanding 'inter-class' differences is not.

Antihistamines are usually categorized as 'classic' or first-generation antihistamines and 'newer' or second-generation antihistamines. The major property that distinguishes these categories is the presence of side effects on the central nervous system (CNS) at standard dose levels. Sleepiness is the most common CNS effect; however, such sleepiness should be understood as a form of general sedation, because antihistamines may also cause cognitive impairment that may interrupt daytime activities requiring concentration and alertness.

The characterization outlined above is limited because it focuses on just one aspect of clinical outcomes. A more important difference from the perspective of clinical pharmacology and therapeutics is that first-generation antihistamines were developed so long ago that many were approved before the establishment of modern regulatory criteria for drug approval. Thus, we have little information regarding the pharmacokinetic-pharmacodynamic (PK-PD) properties of many first-generation antihistamines in humans. This is a major cause of debate regarding the efficacy and safety of antihistamines. Major clinical pharmacologic features of both generations of antihistamines are summarized in Table 1.

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Table 1. Pharmacokinetic and pharmacodynamic characteristics of single-dose oral antihistamines in healthy young adults

Generation	Drug	Onset of action (h)	t_{max} (h)	Half-life (h)	Duration of action (h)	Drug interaction	Dose adjustment
1	Chlorpheniramine	0.5 - 3	2 - 3.6	20 - 36	24	Possible	NA
	Clemastine	2	NA	10 - 12	NA	Possible	NA
	Diphenhydramine	2	0.7 - 2.7	7 - 11	12	Possible	H
	Hydroxyzine	2	1.7 - 2.5	16 - 24	24	Possible	H
2	Cetirizine	1 - 3	0.5 - 1.5	7 - 10	≥ 24	Unlikely	H, R
	Desloratadine	2	1 - 3	27	≥ 24	Unlikely	H, R
	Ebastine	2	1.5*	10 - 20*	≥ 24	Possible	H, R
	Fexofenadine	2	2.5	14	24	Unlikely for CYP Possible for p-glycoprotein	R
	Levocetirizine	NA	0.3 - 1.3	5.5 - 8.5	≥ 24	Unlikely	H, R
	Loratadine	1 - 3	0.9 - 1.5	12 - 15	24	Unlikely	H, R
	Mizolastine	1	1.5	13	24	Possible	H

t_{max}, time between oral administration and peak plasma concentration; NA, No available information; H, Hepatic impairment; R, Renal impairment
*With >50% coefficient of variation

Recently-developed, new antihistamines are typically released in the form of active metabolites or enantiomers of second-generation antihistamines. These are conventionally called 'third-generation' antihistamines. However, the definition of third-generation antihistamines remains unclear, and lower CNS effects or lower cardiotoxicity potential in comparison to second-generation antihistamines are inconsistently used as distinguishing criteria.[8]

Clinical pharmacokinetics

The pharmacokinetics (absorption, distribution, metabolism, and elimination) of many first-generation antihistamines have never been fully investigated during clinical trials. Fortunately, knowledge about essential pharmacokinetic properties needed to determine dosage regimens, such as time to maximum plasma concentration attainment and elimination half-life, is sufficient for widely used agents due to clinical studies that were undertaken after marketing approval.[11,12] In addition, many human PK studies were conducted in special populations such as infants, children, the elderly, and patients with renal or hepatic impairment.[13,14] Drug-drug interaction (DDI) information was also obtained to assess clinical necessity.[15] However, additional studies are required for food and herbal medications.

PK properties of most second-generation antihistamines were well-characterized during their clinical development and similar to those of first-generation antihistamines for the following reasons: 1) first-generation antihistamines have acceptable PK profiles to be used for targeted indications, 2) second-generation antihistamines were developed not to improve PK properties but to improve toxicity profiles and reduce side effects, particularly CNS effects.[16]

In general, antihistamines are rapidly absorbed and the effective plasma concentration is attained within 3 hours (at maximum) followed by maximum plasma concentration within 1 hour thereafter. Since most antihistamines act upon the substrate of CYP3A4, grapefruit juice increases the bioavailability of the drugs by inhibiting drug metabolism in intestinal mucosa.[17] Once absorbed, most antihistamines undergo hepatic metabolism by several cytochrome p450 (CYP) isoenzymes, with exceptions such as cetirizine, levocetirizine (urinary excretion), and fexofenadine (fecal excretion). Thus, these drugs have considerable DDI potential with other drugs sharing the same metabolic pathways and/or affecting enzymatic activity and may be influenced by the genotypes of CYP genes.[17] Fortunately, the Korean population is relatively homogeneous in terms of CYP3A4 and CYP2D6 genotypes, so the influence of genotype variation may be less than in other populations.[18-20] The elimination half-life ranges from about 6 hours for cetirizine, levocetirizine, and loratadine to 27 hours for desloratadine. Most antihistamines have elimination half-lives shorter than 16 hours.[16]

Clinical phamacodynamics

Antihistamines show instantaneous concentration-response relationships,[1,9,21] which means the drug effect is altered in the same manner as the time course of plasma concentration changes. Thus, the onset of drug action occurs within 1-2 hours after oral administration regardless of antihistamine generation.

Table 2. Side effects of antihistamines according to the blocked receptors

H1 (histamine) receptor	Muscarinic receptor	α- adrenergic receptor	Serotonergic receptor	Cardiac channels
↓ CNS neurotransmission	urinary retention	hypotension (postural)	↑ appetite	QT prolongation
Sleepiness	sinusoidal tachycardia	dizziness		Ventricular arrhythmia
↓ cognitive function		reflex tachycardia		
↑ appetite				

Despite insignificant differences in elimination half-life between generations, the duration of action tends to be longer in second-generation antihistamines (>24 hours). This duration facilitates once-daily dosing of second-generation antihistamines, while first-generation antihistamines must be administered 2-3 times a day. Increased potency may explain this therapeutic improvement. Tolerance to the effects of second-generation antihistamines does not occur with regular daily dosing.[1]

Antihistamines show low specificity in their binding targets. This leads to different side effects depending on the binding target (Table 2). Patient response and occurrence of adverse drug reactions vary greatly between classes and between agents within classes.[22,23] Thus, if a patient suffers from side effects of a particular antihistamine agent, the primary healthcare provider should consider prescribing another kind of antihistamine agent. Second-generation antihistamines have high affinity and selectivity for the peripheral H1 receptor, and lower binding affinity for the cholinergic (muscarinic) and α-adrenergic receptor sites than do first-generation antihistamines.[8,23] Specificity for the peripheral H1-receptor site avoids the potential for adverse effects on the CNS. Antimuscarinic effects have not been reported for most second-generation antihistamines.

Some antihistamines show the residual action which is defined as persistent pharmacologic effects for days after the discontinuation of treatment. Due to this characteristics, antihistamines should be stopped 5-6 days before allergen skin tests or inhalation challenge tests.[15,21]

Pharmacodynamic interactions may occur between first-generation antihistamines and alcohol, which have synergistic effects on each other's sedative action.[24]

Clinical effectiveness by target disease

The clinical effectiveness of antihistamines as histamine antagonists or inverse agonists is similar regardless of generation, specific agent, or even target disease. However, second-generation antihistamines are preferred for the following advantages over the first-generation agents: 1) more clinical information (e.g., large-scale randomized clinical trial data) is available for these drugs, which makes them more reliable, 2) they have longer durations of action, which improves compliance, and 3) they have lower incidences of side effects, which allows regular continuation of drug therapy. Second-generation antihistamines are the drugs of first choice for the treatment of allergic rhinitis and allergic conjunctivitis (conditions that are frequently combined), as well as for chronic urticaria. For these conditions, the effectiveness of antihistamine treatment is clearly improved when antihistamines are used on a regular basis rather than on an as-needed basis. Nevertheless, the roles of first-generation antihistamines are still emphasized for their anticholinergic and CNS effects, which were once considered simply as "side effects".

Allergic Rhinoconjunctivitis

Oral antihistamines (which are all second-generation antihistamines, as first-generation antihistamines are no longer recommended for the treatment of allergic rhinitis) show clear benefits for preventing and relieving early responses to allergens such as sneezing, nasal and conjunctival itching, rhinorrhea, tearing, and conjunctival erythema.[25-28] They exert not only antiallergic actions, but also anti-inflammatory actions. However, they have only limited effectiveness on late allergic response (e.g., nasal congestion). To overcome this problem, fixed-dose combinations of antihistamine agents with pseudoephedrine or other decongestants may be used. However, no evidence exists to indicate that these combinations have superior effectiveness compared to single antihistamine agents.[4,8,29] When ophthalmic symptoms are predominant, the use of ophthalmic formulations for topical administration is recommended as they have more rapid onset of action. Side effects caused by the systemic absorption of ophthalmic or intranasal antihistamine formulations are minimal according to many clinical studies.[1]

Urticaria and Atopic Dermatitis

Antihistamines are thought to be effective for the treatment of acute and chronic urticaria, including urticarial conditions of physical origin (e.g., cholinergic, cold, aquagenic, and delayed pressure-induced).[1,3] Second-generation antihistamines have demonstrated their clinical benefit through large-scale clinical trials before marketing approval, particularly for chronic urticaria.[30] However, little information is available for first-generation antihistamines, which is why second-generation antihistamines tend to be the drug of choice. Despite limited evidence regarding effectiveness and the risks of side effects, first-generation antihistamines also remain in widespread use for the treatment of chronic urticaria because they are widely available

and less expensive than second-generation drugs.

For the treatment of atopic dermatitis, the drugs of choice are not antihistamines but topical corticosteroids.[31,32] However, first-generation antihistamines administered at night may be helpful for patients with sleep disturbances due to severe pruritus because they have short durations of action (therefore acting only at night) and sedative effects (that help induce sleep).

Common Cold and Chronic Cough

First-generation antihistamines are frequently used for the symptomatic relief of the common cold. Primary health care providers may expect not only antihistaminergic activity but also anticholinergic activity upon prescription of these agents. Unfortunately, a recent large-scale meta-analysis concluded that the clinical effectiveness of first-generation drugs does not outweigh the risk of side effects (sedation).[33] Second-generation (non-sedating) antihistamines have fewer side effects, but lack convincing evidence of efficacy. In addition, fixed-dose combination products containing antihistamines with decongestants are not prescribed for small children due to the risk of overdose. Although the use of these products may be convenient for symptom management in adolescents and adults, it is still unclear that they provide superior risk-benefit profiles compared to single antihistamine agents.[3]

Antihistamines can be used to treat any conditions causing chronic cough including asthma. They are more helpful when the disease entity is allergic rather than cholinergic (e.g., exercise-induced). However they are not the drug of choice for dry, irritating cough as they may thicken the sputum.

Insomnia

Some antihistamines, especially diphenhydramine and doxylamine, are used as sleeping pills for their CNS effects in patients complaining occasional sleeplessness. However, they are not recommended for the treatment of chronic insomnia due to insufficient data for efficacy and safety.[34]

Special population considerations

Infants and Young Children

The safety and efficacy of first-generation antihistamines have never been adequately studied in this population; thus, optimal dose regimens have not been established for most of these antihistamines. Many physicians prescribe first-generation antihistamines for similar indications as those in adults based upon empirical studies. However, they should be prescribed very cautiously for infants and children because juveniles are more susceptible to adverse effects.[8] Moreover, infants and children may even show paradoxical CNS effects that result in excitation of CNS functions, such as aggressiveness, confusion, disinhibition, loss of impulse control, and talkativeness.[1,8] A considerable number of first-generation antihistamines are contraindicated or avoided in infants, and therefore primary healthcare providers should be well-informed regarding drug label information before prescription. For safety, the use of second-generation antihistamines (cetirizine, levocetirizine, fexofenadine, loratadine, and desloratadine) is recommended because their safety (2-3 week duration) in young children was demonstrated in several controlled studies.[35-37]

The Elderly

Primary healthcare providers should always keep the physiologic changes associated with aging in mind. These changes globally influence the PK-PD characteristics of the drugs they use. Antihistamines are no exception in that the elimination half-life and duration of action are prolonged, and sensitivity to sedative (drowsiness, confusion, agitation) and antimuscarinic (mydriasis, dry eyes and mouth, urinary retention) effects is exaggerated in the elderly.[1] In addition, elderly people are usually exposed to polymedication, which results in higher DDI potential than in the younger population. Therefore, the use of second-generation antihistamines is strongly recommended in this age group when they are not prescribed with the intention of sleep induction. Healthcare providers should be careful to avoid decreased daytime performance even when first-generation antihistamines are used as sleeping pills and taken at night. First-generation antihistamines are considered some of the most problematic medications for elderly people.[38]

Pregnancy and Lactation

Currently, no antihistamine agent is classified in pregnancy category A (indicating that adequate and well-controlled human studies have failed to demonstrate a risk to the fetus) or category X (studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits) by the United States (US) Food and Drug Administration (FDA).[1] Most are classified into categories B or C and thus, use of antihistamines during pregnancy depends on risk/benefit assessment. The Korean government applies relatively conservative criteria to determine the availability of individual antihistamines during pregnancy, and several 'cautious' level agents as defined in countries such as the US, the United Kingdom (UK), and Japan are contraindicated in Korea.[39] However, no specific Korean guidelines regarding the use of antihistamines in pregnant or lactating women are available.

Considering recommendations from many publications, the principles of antihistamine use during pregnancy may be summarized as follows (The 5 'A's);

- Always consider whether patients want to use antihistamines, as in many cases, pregnant women are worried about fetal risk
- Administer topical antihistamine agents whenever possible
- Assess whether systemic antihistamines must be used (despite risk)

- Among antihistamine agents, chlorpheniramine, diphenhydramine, cetirizine, levocetirizine, and loratadine are considered to be relatively safe (Category B) for systemic use
- Avoid using antihistamines during the first trimester
  Approximately, 0.1% of oral antihistamine dose is secreted into milk. Thus, some reports indicate that this amount of antihistamine may cause sedation in infants.

Summary

Both generations of antihistamine agents are widely prescribed. However, second-generation antihistamines are generally preferred over first-generation antihistamines when used as drugs of choice for certain indications, mainly due to their improved safety profiles, extended duration of action, and decreased DDI potential, all of which are supported by reliable clinical trial results. Accordingly, the role of first-generation antihistamines has changed, and most uses intentionally leverage their CNS effects, previously considered side effects, for their relatively favorable toxicity profiles compared to other CNS agents. Using first-generation antihistamines to treat patients suffering from the common cold is not recommended. When targeting antihistaminergic activity, second-generation antihistamines should be used for infants, young children, and the elderly. For pregnant women, topical agents should be prescribed whenever possible and systemic administration of only a few relatively safer antihistamine agents should be considered only when the benefits clearly overweigh the risk. As new second-generation antihistamines are developed and marketed, clinicians can expect further improvements in both efficacy and safety.

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