

Clinical pharmacology of new H₁-receptor antagonists, and why it matters

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SUMMARY

There are many new H₁-receptor antagonists. Their clinical pharmacology, as objectively measured in pharmacokinetic and pharmacodynamic studies, differs considerably. The importance of understanding these differences should not be underestimated, as they directly influence H₁-antagonist dose and dose interval, and they facilitate H₁-antagonist use in special populations, for example, the elderly. Without a doubt, pharmacokinetic and pharmacodynamic studies of H₁-antagonists provide a scientific foundation for using these medications with optimal effectiveness and safety.

KEY-WORDS: H₁-receptor antagonists. – Clinical pharmacology. – Cytochrome P450.

RÉSUMÉ

Importance particulière de la pharmacologie clinique des nouveaux antagonistes des récepteur H₁. – Nombreux sont les nouveaux antagonistes des récepteurs H₁. Leur pharmacologie clinique, telle que objectivement mesurée par les études pharmacocinétiques et pharmacodynamiques, varie considérablement. L'importance de la compréhension de ces variations ne doit pas être sous-estimée, car elles influencent directement la dose et la fréquence de l'antagoniste H₁ et elles aident à adapter l'utilisation de l'anti-H₁ à des populations particulières, par exemple les gens âgés. Sans aucun doute les études pharmacocinétiques et pharmacodynamiques des antagonistes H₁ fournissent une base scientifique pour l'emploi de ces médicaments avec la meilleure efficacité et sécurité.

MOTS-CLÉS: Antihistaminiques. – Pharmacologie clinique. – Cytochrome P450.

INTRODUCTION

H₁-antagonists, discovered by researchers in France 60 years ago, continue to be important medications for relief of symptoms in allergic disorders [11]. The attributes of an ideal H₁-antagonist are defined in table I [13]. Understanding the pharmacokinetics and pharmacodynamics of the new H₁-antagonists provides the objective basis for selection of an appropriate dose and dose interval, and the rationale for dose regimen modifications which are needed in special populations.

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PHARMACOKINETICS

The comparative pharmacokinetics of selected H₁-antagonists in healthy young adults are shown in table II [2, 5-10, 14, 15.]. After oral administration, H₁-antagonists are generally well-absorbed, with peak plasma concentrations being reached within a few hours after dosing in fasting patients. Most H₁-antagonists appear to be extensively distributed into body tissues, however, volumes of distribution measured pharmacokinetically are generally uncorrected for bioavailability because intravenous formulations are not available for

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Table I. – The ideal H₁-receptor antagonist.

<i>Pharmacokinetics</i>	
Rapid absorption.	
No accumulation (i.e. no change in pharmacokinetics with repeated dosing over time).	
No medication interactions (eg. when ketoconazole or erythromycin are concomitantly administered).	
No dosage adjustment needed in special populations (eg. those who are very young, very old, or have moderate/severe renal or hepatic dysfunction).	
<i>Pharmacodynamics</i>	
Rapid onset of action.	
Duration of action 24 hours, facilitating once-daily dosage.	
Offset of action within a few days.	
No tachyphylaxis.	

comparison with oral formulations. Many H₁-antagonists are highly protein-bound in the circulation and in tissues. Disposition is characterized by an open two-compartment pharmacokinetic model. Terminal elimination half-life values range from 2-24 hours.

For practical purposes, it is useful to divide the new H₁-antagonists into two groups: those which are not metabolized extensively in the cytochrome P450 system in the liver and gastrointestinal tract, and those which are metabolized more extensively. The first group includes medications such as acrivastine, cetirizine, fexofenadine, and levocabastine [2, 6, 8, 14]. These medications are unlikely to compete for elimination with other medications metabolized in the cytochrome P₄₅₀ system and are also less likely to be implicated

Table II. – Practical pharmacokinetics and pharmacodynamics of representative new H₁-antagonists.

<i>H₁-receptor antagonist (metabolite)</i>	<i>t_{max}¹(hr) after a single dose</i>	<i>Terminal elimination t_{1/2}² (hr)</i>	<i>% Eliminated unchanged in the urine/feces</i>	<i>Drug inter-actions</i>	<i>Duration action (h)</i>	<i>Once-daily dosing</i>	<i>Population in which dose adjustment is required</i>
Eliminated largely unchanged							
Acrivastine	1.4	1.7	59/0	unlikely	8	no (tid)	none
Cetirizine	1.0	7.4	60/0	unlikely	24	yes	GRH
Fexofenadine	2.6	14.4	12/80	unlikely	12-24	yes	none
Levocabastine; intranasal	1-2	35-40	70/20	unlikely	12	no (bid)	R (long-term)
Extensively metabolized							
Astemizole (norastemizole & desmethylastemizole)	0.5 (0.7)	1.1 days (9.5 days)	n/a	high	> 24	yes	H
Azelastine ³ ; intranasal (desmethy lazastine)	2.5	n/a	n/a	unlikely	12	no (bid)	none
Ebastine (carebastine)	(3.6)	(14)	n/a	possible	24	yes	H
Loratadine (descarboethoxyloratadine)	1.0 (1.5)	7.8-11.0 (17-24)	trace	unlikely	24	yes	RH ⁴
Mizolastine ⁵	1.9	12.9	0.5	possible	24	yes	none

Results are expressed as mean + standard deviation. / 1. Time from oral intake to peak plasma concentration. / 2. Terminal elimination half-life. / 3. Orally administered azelastine has a t_{max} of 4.5 hrs; the active metabolite, desmethy lazastine, has a t_{1/2} of 42 hours; and dose reduction is necessary in elderly patients. / 4. In the presence of CYP3A4 inhibition, loratadine is eliminated via the CYP2D6 metabolic pathway. / 5. No active metabolites identified. / bid : twice daily. / tid : three times daily. / G : geriatric. / R : renal function-impaired. / H : hepatic function-impaired.

in causing adverse medication interactions. Fexofenadine is eliminated unchanged in the feces and urine. More than 50 % of a dose of acrivastine, cetirizine, and levocabastine is eliminated unchanged in the urine. Elimination of acrivastine, cetirizine, and fexofenadine may be reduced in patients with impaired renal function, and the elimination of cetirizine may be reduced in patients with either impaired renal or hepatic function.

Other new H₁-antagonists such as astemizole, azelastine, ebastine, loratadine, and mizolastine undergo first-pass hepatic extraction and extensive metabolism in cytochrome P₄₅₀ system; after usual single oral doses, the plasma concentration of the parent compound is low, in contrast to a high concentration of the metabolite(s) [5, 7, 9, 10, 15]. Compared to the values found in healthy young adults, terminal elimination half-life values for these H₁-antagonists are often shorter in infants and young children, and longer in the elderly. Elimination half-life values for these H₁-antagonists may also be prolonged in patients with hepatic dysfunction or in patients concomitantly receiving macrolide antibiotics, imidazole anti-fungals, or other medications which compete for elimination in the cytochrome P₄₅₀ system.

For research purposes, extensive metabolizers and poor metabolizers in the patient population can be identified by phenotyping hepatic cytochrome P₄₅₀ isozymes such as CYP2D6. H₁-antagonist metabolism and medication interactions can also be studied *in vitro* using human liver tissue slices, hepatocytes, hepatoma cells, microsomal preparations, or purified recombinant fusion proteins containing cytochrome P₄₅₀ systems, with some ability to predict the *in vivo* response.

PHARMACODYNAMICS

Pharmacodynamics is defined as the relationship between the plasma concentration of a medication and the intensity of the pharmacological effect produced. Understanding of the dose-response relationship, and the onset, peak, and duration of action of H₁-antagonist activity have been facilitated by objective assessments of suppression of the histamine- or antigen-induced wheal and flare responses in the skin. Using this standardized bioassay, and using allergen challenge tests in subjects with allergic rhinitis, significant differences in H₁-antagonist activity can be identified during the first 24 hours after administration [2, 3, 5-10, 12, 14, 15]. In contrast, clinical evaluations over weeks using subjective symptom scores

in patients with allergic rhinoconjunctivitis or urticaria tend to demonstrate similarities in efficacy and effectiveness among H₁-antagonists [2, 5-10, 14, 15].

Onset of action, peak action, duration of action, and remnance of action,

The pharmacodynamics of H₁-receptor antagonists differ depending on the medication and the dose administered. H₁-antagonist peak concentrations in target organs such as the skin are achieved rapidly after oral administration, and this is reflected in the rapid onset of H₁-antagonist activity, often within an hour [2, 3, 5-10, 12, 14, 15]. Peak suppression of histamine-induced wheals and flares by H₁-antagonists generally occurs 5 to 7 hours after oral administration of a single dose, later than peak plasma concentrations. Maximum H₁-blockade often persists even after plasma concentrations have declined to the lowest limits of analytical detection. This persistent effect is probably due to high tissue/serum concentration ratios, and, for some medications, the presence of active metabolites. Ideally, H₁-antagonists should be given before an anticipated allergic reaction in order to achieve maximum efficacy.

The duration of action of a single dose of an H₁-antagonist, assessed objectively from suppression of the histamine- or allergen-induced wheal and flare in the skin, or subjectively by suppression of symptoms, is even more prolonged than might be expected from consideration of the terminal elimination half-life values, and is at least 24 hours for many H₁-antagonists. The duration of action may be even longer in elderly patients and in patients with hepatic or renal dysfunction, necessitating a reduced dose in these populations.

Most H₁-antagonists need to be discontinued for 2-7 days before allergen skin testing. Astemizole, however, should be discontinued for at least 6 weeks before skin tests or inhalation challenge tests with allergen or histamine.

Lack of subsensitivity to peripheral H₁-blockade

Subsensitivity or loss of effectiveness to the peripheral H₁-receptor blocking activity of H₁-antagonists has not been found in rigorously controlled, double-blind studies of several months duration in which H₁-blockade activity has been monitored objectively using suppression of the skin wheal and flare [1, 5, 10, 11, 13, 14], or in which efficacy has been monitored subjectively as reflected in suppression of perennial rhinitis symptoms [2, 5-10, 14, 15]. The apparent subsensitivity demonstrated in some airway or central

nervous system studies is difficult to explain, as H₁-receptors do not differ in skin, upper and lower airways, and central nervous system.

THE FUTURE

A perfectly effective and safe H₁-antagonist is now within the realm of possibility. Medications which have combined histamine H₁-antagonist and cysteinyl leukotriene antagonist activity, or combined H₁-antagonist and 5-lipoxygenase inhibitor activity, also offer exciting therapeutic possibilities for the future.

Several research groups identified the gene encoding the human H₁-receptor in the early 1990s. Recently a novel polymorphism was discovered in this receptor: a single amine substitution on codon 356 within the third intracellular loop, which is a critical area for receptor phosphorylation⁴. At this time, the therapeutic significance of this polymorphism is unknown, however, using genotyping and phenotyping of the pharmacodynamic response, it may be possible to identify H₁-antagonist responders and non-responders, and direct therapy accordingly.

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