Comparative pharmacology of the H_1 antihistamines

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The United States National Library of Medicine defines the term pharmacokinetics as "the dynamic and kinetic mechanisms of exogenous chemical products, and the absorption, biotransformation, distribution, release, transport and elimination of drug substances according to their dosage and extent and rate of metabolism".

Although the efficacy of the different H_1 antihistamines in the treatment of allergic patients is similar, even when comparing first- and second-generation drugs, they are very different in terms of chemical structure, pharmacology and toxic potential. Consequently, knowledge of their pharmacokinetic and pharmacodynamic characteristics is important for the correct usage of such drugs, particularly in patients belonging to extreme age groups, pregnant women, or subjects with concomitant diseases.

The current requirements of the different drug agencies for authorizing the introduction of a new medication have led to the availability of much more information on the pharmacokinetic and pharmacodynamic characteristics of the second-generation antihistamines than on their first-generation predecessors. It seems that this consideration alone would advise the more widespread use of these more modern antihistamines – in contrast to the evidence supplied by the current sales statistics, which show first-generation antihistamines to be much more widely used.

Curiously, most of the pharmacological aspects of the new antihistamines are difficult to document, and remain largely unpublished – the only source for consultation being the summaries presented by the drug manufacturers at scientific congresses and meetings, or the famous

Table 1. Absorption pharmacokinetics of some antihistamines.

Generation	Drug	Tmax*(hours)	Time to action (hours)**
First	Chlorpheniramine	2.8±0.8	3
	Diphenhydramine	1.7±1.0	2
	Doxepin	2	na#
	Hydroxyzine	2.1±0.4	2
Second	Acrivastine	1.4±0.4	1
	Ketotifen	3.6±1.6	na
	Cetirizine	1.0±0.5	1
	Loratadine/	1.2±0.3	2
	Decarboethoxyloratadine***	1.5±0.7	
	Ebastine/Carebastine***	2.6±5.7	2
	Fexofenadine	2.6	2
	Mizolastine	1.5	1
	Levocetirizine	0.8±0.5	1
	Desloratadine	1-3	2
	Rupatadine	0.75	2

* Time elapsed from administration via the oral route to maximum plasma concentration; ** Based on papule and erythema testing; *** Principal active metabolite. # na, not available. Modified from reference 1.

Table 2. Metabolization pharmacokinetics of some antihistamines.

Generation	Drug	Liver metabolization	Drug interactions	Dose adjustment	Comments
First	Chlorpheniramine	Yes	Possible	na	
	Diphenhydramine	Yes	Possible	Liver failure	
	Doxepin	Yes	Possible	Liver failure	
	Hydroxyzine	Yes	Possible	Liver failure	
Second	Acrivastine	<50%	Improbable	nd	
	Cetirizine	<40%	Improbable	Liver and kidney failure	
	Loratadine	Yes	Scantly improbable	Liver and kidney failure	
	Ebastine	Yes	Possible	Liver and kidney failure	Keto, Erythro
	Fexofenadine	<8%	Yes (P glycoprotein)	Kidney failure	< or > bioavailability
	Mizolastine	Yes	Possible	na	
	Levocetirizine	<15%	Improbable	Liver and kidney failure	
	Desloratadine	Yes	Improbable	Liver and kidney failure	> bioavailability
	Rupatadine	Yes	Improbable	Liver and kidney failure	

Modified from reference 1.

"data on file" that are commonly found in the publicity literature of the different drug products. By consulting these data and the published reviews, the most important aspects in relation to the comparative pharmacology of the different antihistamines can be summarized in the sections below.

Absorption

Most antihistamines show good absorption when administered via the oral route, as is demonstrated by the fact that effective plasma concentrations are reached within three hours after dosing (Table 1) [1]. The good liposolubility of these molecules allows them to cross the cell membranes with ease, thereby facilitating their bioavailability.

Papule and erythema inhibition tests show that the great majority of antihistamines exert an effect upon this skin reaction mediated by histamine within 1-3 hours after oral dosing (Table 1) [2].

In some cases, concomitant administration with food can alter the plasma concentrations of these drugs. This is explained by the presence of active transport mechanisms across cell membranes – the best known of which are P glycoprotein and the organic anion transporter polypeptides. These proteins and polypeptides are located in the cell membrane, and function as active transport systems for other molecules showing affinity for them. In some cases these transport systems act as important elements in drug absorption or clearance, while in other cases they allow tissue detoxification, depending on whether they are located in intestinal cell membranes (in the former case) or at the blood-brain barrier (in the latter case).

Some antihistamines behave as substrates for these active transport systems, such as for example fexofenadine [3], while in other cases drug intestinal absorption is not seen to be affected – as is the case of desloratadine [4]. This may be interpreted as a negative aspect in that it can determine variations in antihistamine bioavailability when coadministered with other substrates of these same active transport systems. On the other hand, a positive aspect is represented by the fact that this mechanism is particularly important in relation to tissue detoxification (i.e., clearance of toxic elements from the central nervous system), as will be seen below. For some antihistamines such as fexofenadine, variations in bioavailability have been documented associated with the combined administration of foods that serve as substrates for P

glycoprotein – such as grapefruit or bitter orange juice [5] – as well as of drugs that have this same property, such as verapamil, probenecid or cimetidine [6].

Metabolization

Liver metabolization. Most antihistamines are metabolized and detoxified within the liver by the group of enzymes belonging to the P450 cytochrome system. Only acrivastine, cetirizine, levocetirizine, desloratadine and fexofenadine [7] avoid this metabolic passage through the liver to an important degree – which makes them more predictable in terms of their desirable and undesirable effects. Cetirizine and levocetirizine are eliminated in urine, mainly in unaltered form, while fexofenadine is eliminated in stools following excretion by the biliary tract, without metabolic changes. The rest of antihistamines undergo liver transformation to metabolites that may or may not be active, and whose concentrations in plasma depend on the activity of the P450 enzyme system. This activity in turn is genetically determined. Some individuals show high intrinsic activity of this enzyme system, while others show lessened activity at baseline. These patients can be identified by studying their expressed liver enzyme phenotype (e.g., CYP3A4 or CYP2D6). The activity of the liver enzyme complex can also be altered under special metabolic conditions such as infancy [8], advanced age [9], liver diseases [10], or by direct drug action upon the enzyme complex [11].

Drug interactions resulting in a decrease in plasma concentration of the drug may lessen its clinical efficacy, as occurs when administering H_1 antihistamines together with cytochrome P450 inducers such as the benzodiazepines [12]. In other cases an increase in plasma concentration of the antihistamine can result, and its adverse effects may thus increase as well. This occurs when coadministering the drug with other P450 cytochrome substrates that competitively inhibit its metabolism, such as the macrolides, antifungals or calcium antagonists [13]. In these cases the safety margin of the antihistamine, i.e., the concentration range for which the incidence of adverse events is minimal, will be a very important consideration, since the plasma levels will be unpredictable. Thus, drug dose adjustment may prove necessary in all the above mentioned situations (Table 2).

Actions on target organs

Antihistamines are present in low concentrations in plasma, and such drug levels are generally not determined on a routine basis. From the pharmacokinetic perspective, the assay methods used have improved in recent years with the introduction of new techniques such as gas-liquid chromatography and high performance liquid chromatography with mass spectrometry (HPLC-MS), which allow the detection of minimal concentrations in plasma and tissues, and the identification of components and their metabolites. A large percentage of the circulating plasma antihistamine concentration is bound to plasma transporter proteins – fexofenadine and acrivastine being the molecules with the lowest percentage binding values (60-70% and 50%, respectively), since the rest of antihistamines are bound over 95% to plasma proteins. However, isolated pharmacokinetic study is of scant interest, and from the clinical point of view it is much more important to conduct pharmacodynamic studies that serve to define aspects such as drug potency, mechanism of action, or toxicity.

Antihistamines act upon histamine receptors at the surface of the different cell types that express them. There are four histamine receptor subtypes: H_1, H_2, H_3 and H_4, of which H_1 and H_2 are extensively expressed by many cells within the body. The H_1 receptor has been associated with many actions in relation to allergic inflammation, such as rhinorrhea, smooth muscle contraction, and many forms of itching (pruritus). This is mediated by the transduction of extracellular signals through G protein and intracellular second messengers (inositol triphosphate, diacylglycerol, phospholipase D and A_2, and increases in intracellular calcium concentration) [14]. Recently there have also been reports of NF-κB transcription factor activation by the H_1 receptors, which would explain the antiinflammatory actions of antihistamines via this route – since the mentioned transcription factor is associated with actions such as the regulation of adhesion molecules, chemotaxis, proinflammatory cytokine production, and antigen presentation [14].

The H_1 receptors belong to the superfamily of G protein coupled receptors (GPCRs), and are encoded for by chromosome 3. The cloning and expression of these elements by recombinant cells has allowed advances in the study of these receptors that have changed our understanding of how they work. We now know that these receptors exhibit spontaneous activation of their intracellular messengers, requiring no binding by an agonist at surface level [15]. This spontaneous activity is referred to as constitutive activity and is attributable to the dynamic balance between two conformations of the receptor – activated (characterized by the production of intracellular second messengers) and inactive (no such intracellular signaling) [16]. This situation has led to reclassification of the drugs that act upon these receptors, according to which of the two receptor conformations are stabilized as a result of their action. In this sense, if the ligand stabilizes the active receptor conformation, making it the predominant form, then the drug is referred to as an agonist, while if the inactive conformation is stabilized the drug is said to be a inverse agonist. In this way, histamine is an agonist, while the antihistamines are presently considered to be inverse agonists [17] instead of antagonists as previously believed (Figure 1). A neutral antagonist would block both receptor conformations on a

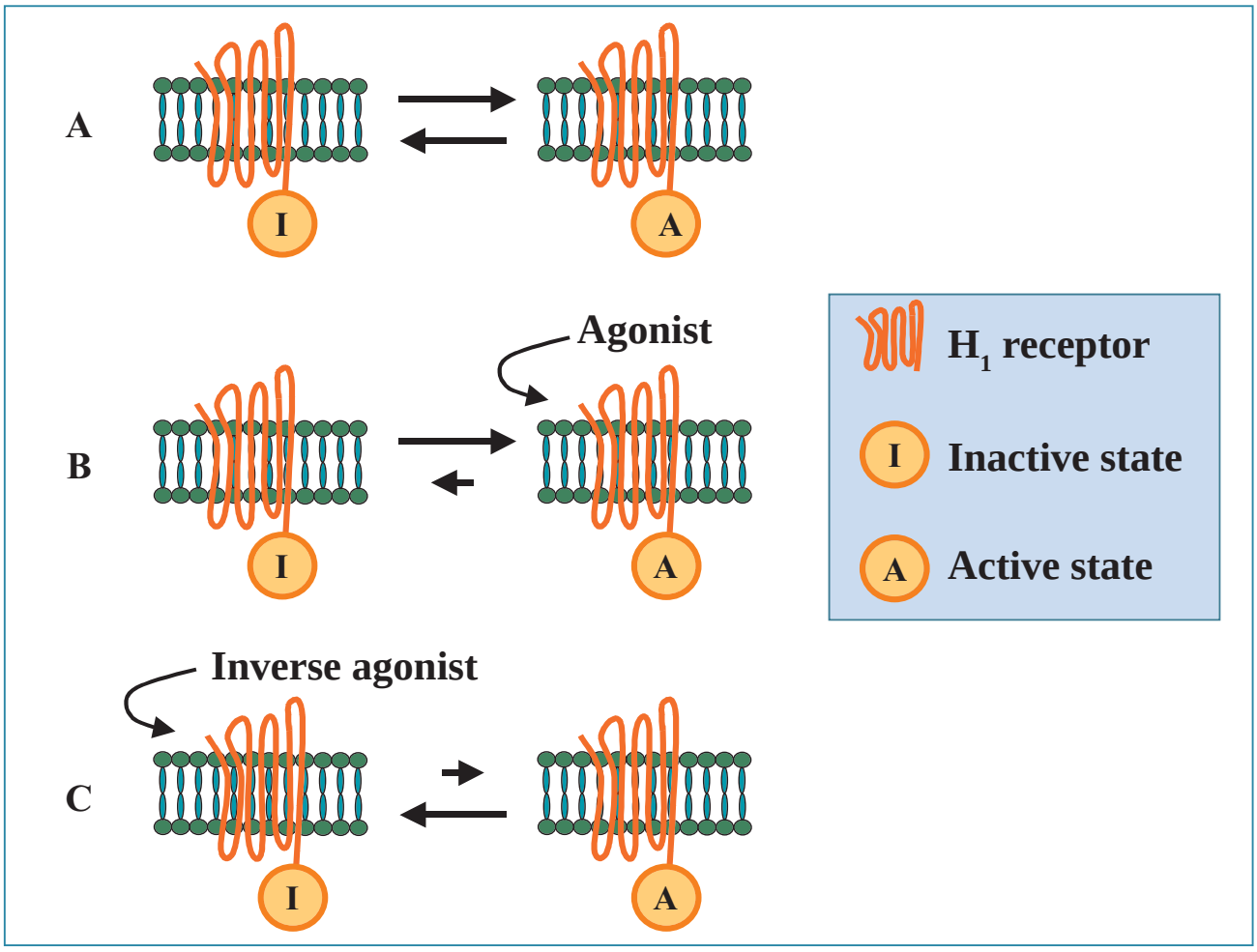

Figure 1. The three different states in which the histamine receptor can be found. Case A: balance between the two conformations; B: predominance of the activated conformation via the action of an agonist; and C: predominance of the inactivated conformation via the action of an inverse agonist. Modified from reference 1.

competitive basis, without altering the dynamic balance or baseline activation of the receptor. The clinical relevance of these findings is still unclear, since no drug is presently available that acts as a neutral antagonist – though it would be interesting to develop different types of antihistamines according to their activity as potent inverse agonists or antagonists. The former would be of interest if the objective were to reduce intrinsic receptor activity, and the latter in the case of seeking continued intrinsic activity while preventing all agonist action [18].

The pharmacodynamic aspects relating to antihistamine actions upon the target organs are studied by means of experimental models, allowing the comparison of different antihistamines and prediction of their therapeutic actions.

Many models have been proposed with this objective in mind – the most widely accepted being the wheal and erythema inhibition test, and the allergic rhinitis model. New models have recently also been proposed, such as the receptor occupation model, which also will be addressed.

- In the wheal and erythema test, objective assessment is made of the intensity of the antihistaminic effect by measuring the inhibition of wheal and erythema formation induced by histamine injection into the skin, after oral dosing of the study drug. Practically all the antihistamines have been studied with this model, inducing significant inhibition of wheal and erythema formation versus placebo, in an intense and constant manner over time. Figure 2 graphically reflects one of the most interesting comparative studies made with this model [2], showing epinastine (not available in Spain) to be the fastest acting antihistamine according to this model, while cetirizine is defined as the most potent. The maximum effect on wheal and erythema formation is reached 5-8 hours after oral dosing, unlike the maximum plasma concentration, which is reached much earlier. However, in the case of most antihistamines, this effect is maintained for longer periods of time (though to different degrees depending

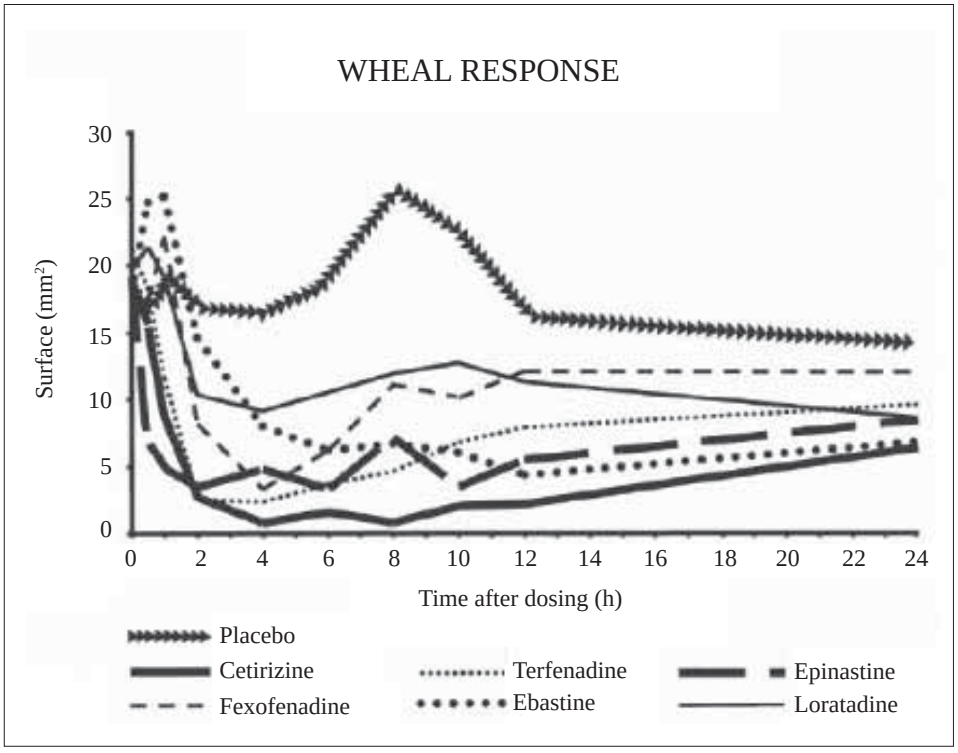

Figure 2. Inhibition of skin wheal formation following the intradermal injection of histamine, and after prior oral administration of different antihistamines. Reproduced with permission from [2].

on the drug involved) than the plasma levels – which decrease in the first few hours after administration via the oral route [19,20]. Thus, fexofenadine and cetirizine maintain inhibitory action due to proportionality between the tissue and plasma drug concentrations strongly in favor of skin concentration, while other antihistamines such as loratadine or ebastine maintain a less potent though still considerable effect thanks to the suggested persistence in skin of their active metabolites.

The allergic rhinitis model is a clinical evaluation based on symptoms scoring in patients diagnosed with allergic rhinoconjunctivitis subjected to intranasal allergen or histamine provocation, followed by evaluation of the capacity of the previously administered study drug to inhibit the response to such provocation [21]. Such testing also must be performed on a randomized basis and with placebo control, in the same way as in wheal and erythema inhibition studies. In addition to the reduction in symptoms score, objective assessment of such inhibition can be established by determining nasal vascular permeability through the measurement of α macroglobulin (in the nasal secretions) [22]. In contrast to the differences detected when using the wheal and erythema test, few clinical differences are observed among the different antihistamines when this model is used. Practically all the new antihistamines present studies based on this test in their authorization registry applications presented to the different drug agencies – the conclusion being that their efficacy is at least equal to that of some other already available and previously authorized antihistamine.

- The receptor occupation model arises from the paradoxical observation that antihistamines with a high *in vitro* affinity (Ki) for the receptor and a very long plasma half-life (t1/2) induce less potent and briefer wheal and erythema inhibition than other antihistamines with *a priori* poorer pharmacokinetic performance. This model proposes receptor occupation (expressed as a percentage) determined 4 and 24 hours after oral administration as pharmacodynamic assessment criterion [23]. The greater receptor occupation, the better the pharmacodynamic behavior of the antihistamine. Such receptor occupation is calculated on the basis of receptor affinity (Ki), the concentration of free antihistamine at the action site (which is close to the free plasma concentration of the antihistamine [C4h and C24h]), and the maximum percentage of binding sites for the antihistamine. The results obtained for the antihistamines desloratadine, fexofenadine and levocetirizine are reported in Table 3.

In relation to the pharmacodynamic particulars of any drug in general, it is also of interest to address the changes that occur as a result of continuous administration. Thus, no loss of peripheral antihistaminic efficacy (tachyphylaxis) has been demonstrated following continuous daily dosing in any of the studies offering sufficient methodological quality and involving follow-up periods of up to 12 weeks, using the wheal and erythema inhibition test as measure of efficacy. Similar results have been obtained in studies using the allergic rhinitis symptoms score system or urticarial lesions as efficacy parameter [7].

The apparent tachyphylaxis reported in some studies in which the efficacy criterion was action upon the lower

Table 3. Receptor occupation for some antihistamines.

Parameter	Desloratadine	Fexofenadine	Levocetirizine
Dose (mg)	5	120	5
Binding to plasma proteins (%)	85	65	91
Free drug C_{4h} (nM)	1	174	28
Free drug C_{24h} (nM)	0.3	1.4	4
$T_{1/2}$ (h)	27	14	8
Ki (nM)	0.4	10	3
Receptor occupation after 4 h (%)	71	95	90
Receptor occupation after 24 h (%)	43	12	57
Maximum wheal inhibition after 4 h (%)	34	100	100
Wheal inhibition after 24 h (%)	32	15	60
Maximum erythema inhibition after 4 h (%)	19	83	89
Erythema inhibition after 24 h (%)	41	35	74

airways or on the central nervous system may have been attributable to the specific study design involved, since the H_1 receptors do not appear to differ in function according to their location [7]. The most important data in relation to the pharmacodynamics of several antihistamines are reported in Table 4.

An important aspect of the pharmacodynamics of a drug is the study of its distribution in the different body compartments. In pharmacokinetic terms, it is desirable for any drug to present the lowest distribution volume (Vd) compatible with the therapeutic objectives, i.e., interaction with the receptors at effective concentrations, avoiding distribution to those organs where the drug is either ineffective or toxic [24]. Most available drugs are extensively distributed throughout the body, as a result of their required liposolubility, which ensures good absorption via the oral route. This implies that the distribution of a drug is usually more extensive than

Table 4. Wheal and erythema inhibition for some antihistamines.

Medication and dose	Wheal and erythema inhibition				Other organs in which pharmacodynamic studies have been made
	Single dose	Continuous administration			
	Time to action (h)	Duration of action (h)	Residual effect after interruption (days) not available	Tachyphylaxis during continuous administration	
Acrivastine 8 mg	0.5	8	not available	no	Nose, eyes, bronchi
Azelastine, nasal	–	–	–	no	Nose
Azelastine, oral 4 mg[a]	4	12	7	no	Bronchi
Cetirizine 10 mg	0.7	>24	3	no[b]	Nose, bronchi
Ebastine 10 mg	1	>24	3	no	Nose, eyes, bronchi
Fexofenadine 60 mg	2	24	2	no	Nose
Levocabastine, topical	–	–	–	no	Nose, eyes
Loratadine 10 mg	3	24	7	no[b]	Nose, bronchi
Mizolastine 10 mg	1	24	not available	no	–
Desloratadine 5 mg	2	>24	7	no	Nose, bronchi, skin
Levocetirizine 5 mg	1	>24	3	no	Nose, bronchi skin

[a] Not available in Spain; [b] Wheal and erythema inhibition data, published with high methodological quality.
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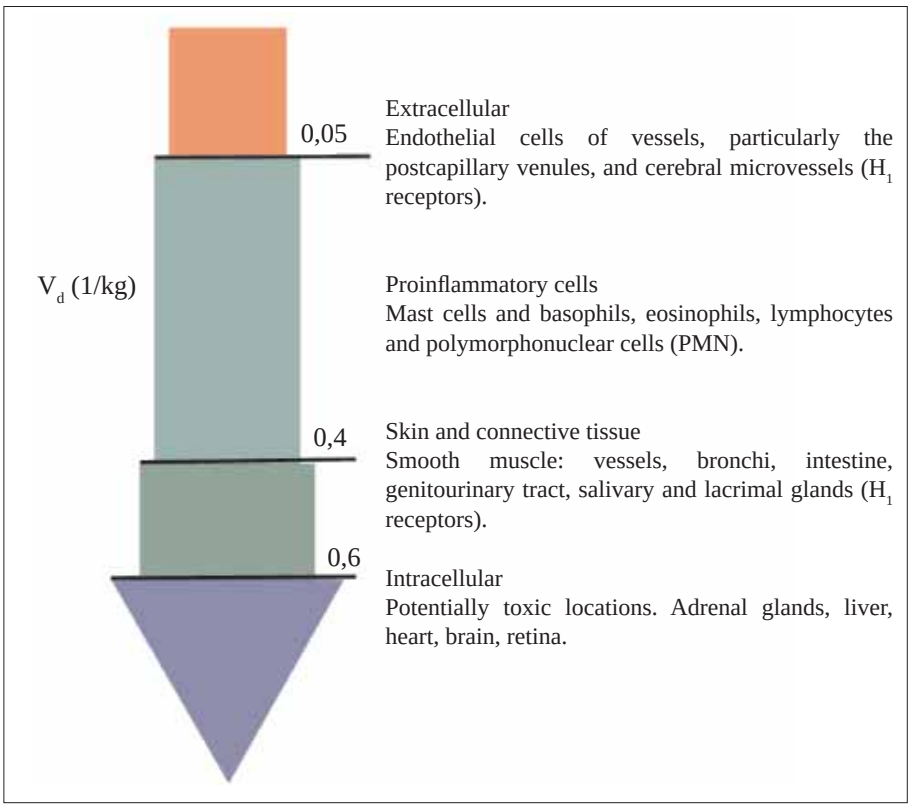

Figure 3. Action sites identified for the most common H_1 antagonists. Reproduced with permission from [24].

strictly required to ensure its therapeutic effect. A low distribution volume can be defined as the exchangeable water volume in the body that is freely and rapidly exchanged between the extracellular and cytosolic compartments. This volume has been calculated as 0.6 l/kg [25]. Distribution volumes far below this value mean that the drug is unlikely to be freed from binding to its plasma transporter protein, thus remaining within the plasma compartment, while volumes far above the aforementioned value mean that the drug extensively binds to cell structures.

Figure 3 provides a schematic representation of action sites according to distribution volume. In general terms, three types of receptors can be differentiated: those located within the cell, such as CYT P450, which is located within the microsomes; those located external to and within the cell membranes, such as the potassium and calcium channels; and finally the so-called surface receptors, such as the 5-HT and H_1 receptors. The H_1 receptors are widely distributed throughout the body, and are found in smooth muscle, endothelial and epithelial cells, eosinophils or neurons. A sufficiently low distribution volume means that the intracellular receptors remain unaffected. Taking into account that the H_1 receptors are easily accessible from the bloodstream, the H_1 antihistamines do not require extensive tissue distribution for correct action. The advantages of a low distribution volume include minimum dose-dependent toxicity for cell and organs, minimum interindividual variations in therapeutic effect, a reduction in undesired drug interactions, and the absence of drug accumulation within the heart or liver. Table 5 reports the distribution volumes of a number of H_1 antihistamines.

Lastly, from the pharmacodynamic perspective, it is important to mention that in addition to distribution of the drug throughout the different body compartments, the development of adverse effects is also conditioned by the presence of the previously commented cell detoxification mechanisms, such as P glycoprotein. Particularly within the central nervous system, it has been demonstrated that P glycoprotein participates in the clearance from this body compartment of antihistamines such as cetirizine [26], carebastine, the active metabolite of ebastine [27], epinastine [28], fexofenadine [3], loratadine [29] and desloratadine [29]. In contrast, it does not contribute to clear first-generation antihistamines or sedatives such as hydroxyzine, tripolidine or diphenhydramine [29]. This could help explain the clear difference in central nervous system side effects on the part of the new antihistamines. Accordingly, status as a P glycoprotein substrate appears to be a desirable characteristic for antihistamines.

Elimination

Most H_1 antihistamines are eliminated through the kidneys after metabolization to a lesser or greater extent. Biliary excretion is also possible, and is more

Table 5. Elimination pharmacokinetics for some antihistamines.

Generation	Drug	Tmax (hours)	Time to of action** (hours)	Duration of action** (hours)	Elimination half-life (hours)	V_d + (L/Kg)	Binding to plasma proteins (%)	Main elimination route	% eliminated without change in urine/stools		Normal adult dose
First	Chlorpheniramine	2.8 ± 0.8	3	24	27.9 ± 8.7	3	72	na	na	na	12 mg /12 h
	Diphenhydramine	1.7 ± 1.0	2	12	9.2 ± 2.5	5	> 95	na	na	na	25-50 mg /8 h
	Doxepin	2	na	na	13	9-33	75-80	na	na	na	25-50 mg /8 h
	Hydroxyzine	2.1 ± 0.4	2	24	20 ± 4.1	13-19	na	na	na	na	25-50 mg /8 h
Second	Acrivastine++	1.4 ± 0.4	1	8	1.4 - 3.1	0.64	50	renal	59	0	8 mg /8h
	Ketotifen	3.6 ± 1.6	na	na	18.3 ± .6.7	56	75	renal	1	na	1-2 mg /12h
	Cetirizine	1.0 ± 0.5	1	24	7-11	0.5	> 95	renal	60	10	10 mg /24h
	Loratadine	1.2 ± 0.3	2	24	7.8 ± 4.2	120	> 95	renal	traces	traces	10 mg /24h
	Decarboethoxyloratadine$	1.5 ± 0.7									
	Ebastine	2.6 ± 5.7	2	24	10.3 ± 19.3	>100	> 95	renal	75-95	0	10-20 mg /24h
	Carebastine$										
	Fexofenadine	2.6	2	24	14.4	5.6	60 - 70	bile	12	80	120-180 mg /24h
	Mizolastine	1.5	1	24	12.9	1.4	> 95	renal	0.5	0	10 mg /24 h
	Levocetirizine	0.8 ± 0.5	1	24	7 ± 1.5	0.4	> 95	renal	86	0	5 mg /24 h
	Desloratadine	1-3	2	24	27	>100	82 - 87	renal	0%	0	5 mg /24h
	Rupatadine	0.75	2	24	5.9	143	> 95	bile	0%	0	10 mg /24h

Tmax: Time elapsed from oral administration to maximum plasma concentration.
** Based on erythema and wheal testing.
+ V_d = Distribution volume in l/kg.
na = Not available
++ Not marketed in Spain
$ Active metabolite.
Modified from reference 1.

Table 6. Pharmacokinetics of some antihistamines under special conditions.

Drug	Advanced age	Liver dysfunction	Kidney dysfunction	Population requiring dose adjustment
Acrivastine	$t_{1/2}$ increases 35%	na	na	None
Cetirizine	Depends on kidney function	$t_{1/2}$ increases to 14 h	$t_{1/2}$ increases to 20 h	Kidney or liver dysfunction, advanced age
Ebastine	na	$t_{1/2}$ increases to 27.2 h instead of 18.7 h	$t_{1/2}$ increases to 23-26h instead of 17-19 h	Liver dysfunction
Fexofenadine	C_{max} increases 68% $t_{1/2}$ increases 10.4%	C_{max} increases $t_{1/2}$ decreases minimally	C_{max} increases $t_{1/2}$ increases to 19--24 h	None (UK) Kidney dysfunction (US)
Loratadine	$t_{1/2}$ increases without clinical relevance	$t_{1/2}$ increases without clinical relevance	$t_{1/2}$ increases without clinical relevance	Kidney or liver dysfunction
Mizolastine	$t_{1/2}$ increases C_{max} decreases	$t_{1/2}$ increases C_{max} decreases	$t_{1/2}$ increases 47%	None

$t_{1/2}$: Elimination half-life; na: Not available; Cmax:: Maximum plasma concentration following a single dose.

extensively applicable to fexofenadine and rupatadine – the former without metabolization and the latter after extensive metabolization. In special cases in which liver or kidney function is impaired, dose adjustment may prove necessary – as in elderly patients or subjects with kidney or liver failure.

Since an antihistamine in combination with a vasoconstrictor (pseudoephedrine) is very common prescription practice, and these drugs are mainly eliminated in urine, it is of interest to determine whether antihistamine excretion is affected when these drugs are administered in combination. This situation has been studied for loratadine – no effects upon the pharmacokinetics of the latter being observed when combined administration is carried out [30]. Likewise, the antihistamines can be eliminated in human milk – an aspect that has been studied for loratadine. In this context, 0.46% of the maternal therapeutic dose is seen to appear in milk [31].

Table 5 summarizes the comparative pharmacokinetics of the different antihistamines. Table 6 in turn reports the modifications in elimination half-life of some H_1 antihistamines, and the dose adjustment requirements in special patient populations.

Conclusions

Although no clinically relevant differences have been described among the different antihistamines in terms of efficacy – even when contrasting the new drugs with the first generation molecules – their evident differences in chemical structure and pharmacology (both kinetics and dynamics) cause the antihistamines to differ among each other from the potential toxicity perspective. As a result, detailed knowledge of these differentiating aspects is needed when deciding to prescribe one antihistamine or other for the treatment of allergic disorders – particularly when the patient belongs to a risk group, such as extreme ages, pregnancy, or in the presence of background disease affecting kidney or liver function.

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