Interactions of the H_1 antihistamines

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An interaction is taken to be the situation in which the administration of a drug or substance induces changes in the pharmacokinetics of another simultaneously administered drug – either increasing or decreasing the plasma concentration of the latter, and thus giving rise to the possibility of adverse reactions [1].

According to the primarily responsible pharmacological mechanism, H_1 antihistamine interactions are fundamentally of a pharmacokinetic nature: the triggering drug or substance induces changes in the absorption and/or metabolism of the H_1 antihistamine [2]. Interactions of a pharmacodynamic nature, i.e., corresponding to those situations in which the actions of the drug or substance upon its target tissues induce modifications in the actions of another drug, have not been reported to date.

The interactions described to date between the H_1 antihistamines and other drugs or substances fundamentally take place via three different routes: the P450 cytochrome system; P glycoprotein (PgP); and the members of the organic anion transport polypeptide (OATP) family.

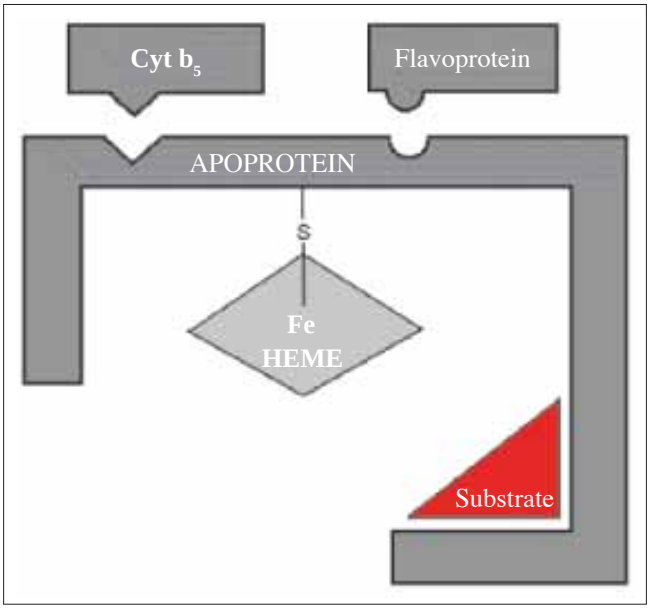

Figure 1. Structure of cytochrome P450: hemoprotein composed of a protein component (apoprotein) and a prosthetic heme group.

Cytochrome P450

Humans are exposed to different foreign and artificially synthesized chemical substances, toxic products of natural origin, or drugs (xenobiotics). In response to such chemical agents, the body does not generate specific degradation and excretion mechanisms for each particular molecule. In a quest for increased efficiency, a general mechanism is used, in charge of eliminating the maximum possible number of molecules from the body at one same time. A system of great functionality and with a broad range of action has therefore been developed: the enzymes belonging to the cytochrome P450 system (Figure 1). These are microsomal enzymes belonging to the family of hemoproteins and which are fundamentally located in the liver cells and enterocytes [3,4]. As a result, the first point of metabolization of drugs or substances that are absorbed from the gastrointestinal tract is the intestine - not the liver.

The enzymes of the cytochrome P450 system are grouped into 14 families of genes with identical sequences, and 17 subfamilies. In global terms, CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 are the most important enzymes in human metabolism [5], while CYP2D6 and CYP3A4 are the most relevant in the specific case of the H_1 antihistamines [6].

Some forms of cytochrome P450 are expressed on a constitutional basis, while others are expressed depending on the sex of the individual or the tissue in which they are located. In turn, some are differentially expressed during development, while others can be induced by chemical substances, environmental pollutants, etc. This combination of factors, and the existence of multiple forms of cytochrome P450, contribute to

establish enormous interindividual variability. In the concrete case of CYP3A4 and CYP2D6 [7,8], a number of studies show their expression to be influenced by environmental factors, as a result of which their activity shows great interindividual variability. In the case of the H_1 antihistamines, and more specifically of terfenadine and loratadine, great interindividual variability has been shown in their liver metabolism mediated by cytochrome P450 [9,10].

Accordingly, it seems that patients with diminished cytochrome P450 activity are at an increased risk of developing toxic concentrations of those substances that are metabolized via this pathway, even at doses within the therapeutic range, and without the need for concomitant interaction with other substances that inhibit this metabolic pathway.

Another point to be stressed is that drugs or other substances are not only able to act as cytochrome P450 substrates (i.e., they can be metabolized by this enzyme system), but can also act as inducers or inhibitors of cytochrome P450 (i.e., respectively increasing or decreasing the enzyme activity of the system). Table 1 summarizes the principal drugs that behave as CYP3A4 substrates, inducers, or inhibitors.

P glycoprotein

P glycoprotein (PgP) constitutes a natural detoxification system expressed in normal human tissues that possess secretory or barrier functions. The system has been developed in the small and large bowel, biliary canaliculi, proximal tubules of the kidney, vascular endothelial cells of the central nervous system, placenta, adrenal glands and testicles [11].

PgP acts as an extracting pump, involving a mechanism that has not been fully elucidated, though it is postulated that drugs or other substances pass through a hydrophobic pore structure composed of a transmembrane domain, requiring an energy-dependent conformation change in the protein structure. A second hypothesis proposed to explain how PgP is able to reduce drug concentrations is that an indirect mechanism is involved, via the regulation of pH and/or electric gradients.

Studies of PgP expression in turn have identified the existence of polymorphisms [12,13].

PgP activity is saturated at high concentrations of the drug or of the substance that transports the latter. This explains why the fundamental importance of the system centers on those locations where drug concentration is lower, such as in plasma – where this regulatory function can be carried out by excreting the drug at kidney or bile level, etc., or by preventing the drug from crossing the blood-brain barrier (BBB) [14].

PgP is presently accepted to be an important factor in the distribution and excretion of drugs, and in drug interactions [15,16].

An interesting point is that some drugs or substances that act as substrates or modulators of PgP activity exert the same functions in relation to CYP3A4 or OATP. These factors must be taken into account as elements possibly predisposing to interactions. Table 2 summarizes the

Table 1. Substrates, inhibitors and inducers of the CYP3A4 isoenzyme.

Substrates		Inhibitors	Inducers
Acetaminophen	Lansoprazole	Cimetidine	Carbamazepine
Alfentanyl	Lidocaine	Clarithromycin	Dexamethasone
Alprazolam	Loratadine	Clotrimazole	Phenobarbital
Amiodarone	Lovastatin	Erythromycin	Phenytoin
Amitriptyline	Midazolam	Fluconazole	Rifampicin
Astemizole	Nefazodone	Fluoxetine	Sulfadimidine
Carbamazepine	Nelfinavir	Fluvoxamine	Sulfinpyrazone
Cisapride	Nifedipine	Gestodene	Thiazolidinedione
Cyclophosphamide	Quinine	Itraconazole	Troleandomycin
Cyclosporine	Rupatadine	Ketoconazole	
Dapsone	Saquinavir	Miconazole	
Digitoxin	Sertraline	Naringenin	
Diltiazem	Tamoxifen	Nefazodone	
Ebastine	Terfenadine	Paroxetine	
Erythromycin	Testosterone	Quinine	
Ethinylestradiol	Theophylline	Ritonavir	
Etoposide	Triazolam	Saquinavir	
Flutamide	Troleandomycin	Sertraline	
Imipramine	Venlafaxine	Troleandomycin	
Indinavir	Verapamil	Zileuton	
Ketoconazole	Warfarin		

Table 2. Interactions of some drugs / xenobiotics with cytochrome P450 and P glycoprotein.

Drug / substance	Cytochrome P450	P glycoprotein
Azithromycin	Slight inhibition of CYP3A4	Substrate / inhibitor
Cimetidine	Inhibition of several isoenzymes	Substrate
Digoxin	Substrate	Substrate
Erythromycin	CYP3A4 inhibitor	Substrate / inhibitor
Fluoxetine	CYP2D6 inhibitor	Substrate
Grapefruit juice	CYP3A4 inhibitor	Inhibitor
Itraconazole	CYP3A4 inhibitor	Substrate / inhibitor
Ketoconazole	Inhibition of several isoenzymes	Inhibitor
Rifampicin	Inducer of several isoenzymes	Inducer
Ritonavir	CYP3A4 inhibitor	Inhibitor / inducer
Verapamil	CYP3A4 substrate / inhibitor	Substrate / inhibitor / inducer

interactions of some drugs or substances with cytochrome P450 and PgP.

Organic anion transporter polypeptide (OATP)

The members of this family that have been identified in humans include OATP-A, fundamentally expressed in brain endothelial cells; OATP-B with a broad distribution in numerous tissues such as the intestine and liver; and OATP-C and OATP-8 with expression in the liver only [11].

Their function is to participate in the distribution and excretion of drugs and other substances in the same way as PgP, though generally in the opposite direction. The xenobiotics that act as substrates for OATP can also serve as substrates for PgP; consequently, they may constitute a key factor in the appearance of interactions [17,18].

First generation H_1 antihistamines

The first generation (or classical) H_1 antihistamines are lipophilic, and are classified into different groups according to their chemical structure. All of them are metabolized by cytochrome P450 in the liver, and they do not function as substrates of PgP [19,20].

Although not all the metabolic routes are fully known, the majority of the classical H_1 antihistamines are metabolized by the CYP2D6 isoenzyme, and some also by CYP3A4 [19,21].

Based on studies using diphenhydramine as a model, the first generation H_1 antihistamines are not only substrates of CYP2D6 but moreover also inhibit the latter. This must be taken into account when such drugs are co-administered with substances that likewise require metabolization via cytochrome P450, such as metoprolol, tricyclic antidepressants, antiarrhythmic drugs, antipsychotics and tramadol [22,23].

Second generation H_1 antihistamines

The second generation H_1 antihistamines, which have been developed in the last 20 years, offer advantages with respect to their first generation counterparts, such as a lesser anticholinergic or sedative effects. However, some of them are not without sporadic or very sporadic side effects, secondary to interactions with other drugs or substances.

The interactions occurring at metabolic level in relation to the second generation H_1 antihistamines such as terfenadine, astemizole, loratadine, desloratadine, ebastine, fexofenadine, cetirizine, levocetirizine, mizolastine, rupatadine and epinastine have been extensively studied since the first report of severe cardiac arrhythmic associated with the administration of terfenadine [24].

In general terms, it may be affirmed that the second generation H_1 antihistamines are PgP substrates [25] – hence their much lesser sedative effects compared with the first generation drugs. In turn, some of the second generation antihistamines undergo important first-step metabolization in the liver or intestine, mediated by cytochrome P450, as will be commented below.

Cytochrome P450 and pharmacological interaction with H_1 antihistamines

The role of CYP3A4 in the metabolism of H_1 antihistamines has drawn considerable attention since the first report that terfenadine can induce serious cardiac arrhythmia when co-administered with CYP3A4 inhibitors such as erythromycin and ketoconazole [26,27].

Posteriorly, other substrates and/or inhibitors of CYP3A4 such as fluoxetine [28], troleandomycin [29] and zileuton [30], among other substances, were investigated to evaluate their interaction with terfenadine - the latter being seen to increase its plasma levels as a

result. In contrast, when terfenadine is co-administered with CYP3A4 inducers such as the thiazolidinediones, its plasma levels may decrease as a result of increased metabolization mediated by this P450 isoenzyme [31,32].

Terfenadine undergoes complete first-step metabolization in the liver via CYP3A4: this metabolization within the liver yields a number of inactive metabolites, together with fexofenadine, which is an active metabolite [33].

Fexofenadine in turn is not metabolized by cytochrome P450, and over 95% of the molecule is recovered in urine and stools [34]. It therefore does not interact with CYP3A4 inhibitors or with any other isoenzyme. Fexofenadine has been shown to be a H_1 antihistamine with a high safety profile, since it lacks cardiological side effects, even at high doses [35,36].

Astemizole has also been implicated in the induction of severe ventricular arrhythmias (torsades de pointes, TdP) when administered at high doses [37,38], or when co-administered with P450 enzyme inhibitors – fundamentally CYP3A4 isoenzyme inhibitors – such as ketoconazole [39] and erythromycin [40]. Although the process by which this occurs is not fully clear, some metabolites may contribute to this pathological cardiac response. Astemizole undergoes complete first-step metabolization in the liver, fundamentally via CYP3A4 [41], yielding different metabolites as a result. Some of these metabolites are pharmacologically active [42,43].

Loratadine also undergoes important first-step processing in the liver, since it suffers almost complete metabolization by cytochrome P450, forming a range of metabolites [44]. One of these metabolites is desloratadine, which after further metabolization in turn yields an active metabolite called decarboethoxyloratadine. Its formation is mediated by both CYP3A4 and CYP2D6 [45].

On the basis of its liver metabolism, loratadine is a candidate for pharmacological interactions with other drugs that are metabolized by cytochrome P450.

Increases have been observed in the plasma concentration of loratadine when co-administered with CYP3A4 inhibitors such as erythromycin, ketoconazole, clarithromycin and cimetidine [46-48]. However, although there is a rise in the plasma levels of the drug, this does not seem to imply any cardiac complication, as revealed by the study of Kosoglou et al [49]. This is in contrast to the observations of Abernethy et al [50], who reported a prolongation in the QTc interval when loratadine was co-administered with a potent CYP3A4 inhibitor such as nefazodone. In any case, the conclusions drawn from the study of Abernethy et al have been questioned from the moment when Barbey, one of the co-authors of the work published by Abernethy, wrote a letter to the same scientific journal that published the work of Abernethy questioning the validness of the results due to the methodology employed and the statistical analysis made [51].

Although desloratadine when co-administered with inhibitors of cytochrome P450 (principally via CYP3A4; erythromycin and ketoconazole) shows a slight increase in its plasma concentrations [52], no adverse electrocardiographic effects have been recorded [53,54].

Ebastine is chemically related to terfenadine, and in the same way as the latter, it is totally transformed mainly via CYP3A4 to yield metabolites of which one is an active metabolite: carebastine [55].

When ebastine is co-administered with a CYP3A4 inhibitor, its plasma levels are seen to increase [56]. This may result in altered electrocardiographic activity – hence the required consideration of the arrhythmogenic potential of the drug [57,58].

Mizolastine undergoes extensive transformation in the context of its metabolization via glucuronidation [59], with scant participation on the part of cytochrome P450. The resulting components are mainly eliminated as conjugates without transformation into active metabolites [60]. The plasma concentrations of mizolastine when co-administered with erythromycin or ketoconazole are high – though without relevance in relation to cardiac electrical activity [61-63].

Epinastine, a H_1 antihistamine marketed in Spain only as eyedrops, does not undergo liver metabolization. As a result, it does not interact with liver cytochrome P450 inhibitors or inducers [64], and is moreover without cardiac adverse effects [65].

Cetirizine is a carboxylic acid metabolite of hydroxyzine. It does not undergo liver metabolization, and therefore does not interact with other drug substances via cytochrome P450 [66,67]. Likewise, no electrocardiographic effects have been observed in patients administered 6 times the recommended dosage [68].

Cetirizine is a racemic R and S enantiomer mixture. Levocetirizine, the S enantiomer of racemic cetirizine, obviously also does not undergo liver metabolization, and likewise no cardiac adverse effects or interactions with other drug substances have been documented [11,69].

The H_1 antihistamine rupatadine is metabolized by cytochrome P450 in the liver, and undergoes interactions with drugs that inhibit this enzyme system – its plasma levels increasing as a result. However, no cardiac side effects have been documented [70].

In the same way that the first generation H_1 antihistamines inhibit CYP2D6, there have been reports of second generation H_1 antihistamine inhibitory action upon the cytochrome P450 system. This is the case for example of loratadine in relation to the CYP2C19 isoenzyme, or of terfenadine, astemizole, cetirizine and mizolastine [71] – though this does not appear to have implications in terms of the appearance of interactions.

P glycoprotein and pharmacological interaction with H_1 antihistamines

The plasma concentration of H_1 antihistamines can be altered by the presence of PgP inhibitors such as

ketoconazole, cyclosporine or verapamil; of PgP substrates and inhibitors such as erythromycin, azithromycin, verapamil or itraconazole; or of PgP inducers such as verapamil or rifampicin [72] – since most (if not all) of them are PgP substrates to one degree or other.

Fexofenadine is a potent PgP substrate, and as such much of its bioavailability and clearance depend on this transport system [11]. Drugs or substances that are able to induce PgP, such as rifampicin, yield a lesser concentration of fexofenadine when co-administered with the latter drug; pharmacological interaction therefore exists in this case. The result of this interaction is a decrease in fexofenadine efficacy [34].

Loratadine may act as both a substrate and potent inhibitor of PgP, though to a lesser degree than verapamil or cyclosporine; the possibility of pharmacological interactions therefore exists [73].

The interaction of desloratadine with other drugs at PgP level cannot be ruled out, since it is a PgP substrate even though it does not inhibit the latter; it therefore does not seem responsible for possible interaction [73,74].

The information on mizolastine is scarce and limited to an increase in plasma levels of digoxin – a typical PgP substrate. Consequently, mizolastine would appear to behave as a PgP inhibitor [75].

Levocetirizine is a weak PgP substrate, it being unlikely for the drug to interact with other substances at this level, according to the study model involved (Caco-2 cells). The same consideration applies to cetirizine [76]. However, cetirizine has also been investigated in another model (a murine model involving the canceling of PgP expression), showing it to be a clear PgP substrate [77]. As a result, possible interaction with other drugs at this level acquires increased relevance.

Terfenadine and ebastine have shown their PgP inhibitory effect and capacity to interact with other drugs that function as PgP substrates; they may thus revert multipharmacological resistance [78,25].

Organic anion transport polypeptide (OATP) and pharmacological interaction with H_1 antihistamines

The role of OATP in the pharmacokinetics of H_1 antihistamines has been examined mainly in application to fexofenadine and desloratadine.

In this context, fexofenadine is a substrate of OATP-A, while desloratadine is not [17,79]. When fexofenadine is co-administered with a PgP inhibitor, the levels of the former increase three-fold in plasma.

Likewise, when fexofenadine is co-administered with probenecid (an OATP inhibitor), its plasma concentrations increase significantly at the expense of a diminished kidney clearance [80]. Therefore, pharmacological interaction is seen to occur at the level of this particular transport system, though the observed effects are difficult to justify in terms of this mechanism alone.

Interaction of H_1 antihistamines with food

In the same way that H_1 antihistamines can interact with other drugs at metabolic level, they can also do so with elements found in food.

It is known that the concomitant ingestion of grapefruit juice increases the plasma levels of certain drugs such as cyclosporine, calcium antagonists and benzodiazepines, among others [81]. This effect is attributable to the capacity of grapefruit juice to inhibit CYP3A4 at intestinal level [82] (this isoenzyme conforming 70% of the total enzymes of cytochrome P450 located in the intestine, and 30% of the activity of the system in the liver [83]). Intestinal CYP3A4 constitutes the first-step transformation point in the metabolization of certain drug substances, such as the H1 antihistamines.

It is therefore to be expected that grapefruit juice is able to increase the bioavailability of H_1 antihistamines through interaction at intestinal level – interaction within the liver being of scant relevance [82,84].

Grapefruit juice has also been shown to induce PgP at intestinal level; therefore, drugs which are substrates for this particular transport system could experience a decrease in bioavailability as a result of such interaction [85,86].

The grapefruit juice components that appear to be implicated in such interactions include flavonoids and furanocoumarins. The flavonoid naringin, which is specific of grapefruit juice, exerts an inhibitory effect upon CYP3A4, mediated by its active metabolite naringenin, as established by the results of *in vitro* studies [87], though these findings are not as conclusive as those obtained from *in vivo* studies. In the group of the furanocoumarins, bergamottin has also been shown to be a potent CYP3A4 inhibitor [88]. However, there are data showing that bergamottin is not the key element in the interaction of grapefruit juice with drug substances at CYP3A4 level [89]. Possibly, grapefruit juice-mediated first-step inhibition of metabolism at intestinal level may be attributable to the combination of flavonoids and furanocoumarins [86].

Grapefruit juice has shown interaction with terfenadine to a degree similar to that observed with itraconazole or erythromycin [90].

The other H_1 antihistamines metabolized via CYP3A4, such as ebastine or loratadine, are also potentially able to interact with grapefruit juice [86].

While fexofenadine is not metabolized by CYP3A4, interaction does exist at PgP level, and particularly at OATP level; consequently, the co-administration of fexofenadine and grapefruit juice gives rise to a drop in drug plasma concentration – an effect also observed with orange and apple juice [17,18].

In the case of desloratadine, no interaction with grapefruit juice has been reported [91].

Among the interactions of the H_1 antihistamines with foods, descriptions have also been made of the inhibition

of astemizole metabolism at CYP3A4 level when the drug is administered with tonic water. The component responsible for this interaction between astemizole and tonic water is quinine, present in the latter [92]. Such interaction results in electrocardiographic alterations secondary to QT interval prolongation [93].

Conclusions

Most first generation H_1 antihistamines inhibit cytochrome P450 (fundamentally isoenzyme CYP2D6), and are able to alter the metabolism of other drug substances that are detoxified via this pathway, such as for example venlafaxine, tricyclic antidepressants, beta-blockers, antiarrhythmic drugs, and tramadol. The second generation antihistamines such as terfenadine or astemizole have demonstrated cardiotoxic potential when their plasma concentrations are elevated secondary to interaction with other drugs – fundamentally at CYP3A4 level. Such effects may even be observed as a result of interaction with certain foods, such as grapefruit juice. Fexofenadine, desloratadine, cetirizine, levocetirizine and rupatadine have shown no cardiotoxic effects when their plasma levels are increased as a result of interaction with drugs or fruit juices at CYP3A4, PgP and/or OATP level. In the case of loratadine, a study has shown its negative effect upon cardiac electrical activity (prolongation of the QT interval) when its plasma levels are raised as a consequence of co-administration with drugs exerting potent inhibitory effects upon isoenzyme CYP3A4 or CYP2D6. Other studies have obtained opposite results, however. None of the second generation H_1 antihistamines inhibit or induce isoenzyme CYP3A4.

To summarize, it can be affirmed that the inhibition of isoenzymes CYP3A4 and CYP2D6 by other drug substances that are co-administered with second generation H_1 antihistamines can give rise to interactions with potentially serious clinical implications – though only in exceptional cases.

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