

The metabolic profile of second-generation antihistamines

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Introduction

The second-generation H₁ antagonists, which have been developed over the past 20 years, have major advantages over the earlier drugs; most notably, less sedation and fewer anticholinergic side-effects. Therefore, they are considered to be a significant pharmacologic advance in the treatment of allergic disorders. However, concern has arisen about the potential of some of these newer drugs to cause serious ventricular arrhythmia (torsade de pointes). Metabolic profile and susceptibility to drug interactions have been identified as risk factors in the development of this rare but life-threatening cardiac side-effect. This paper reviews the metabolism of second-generation H₁ antagonists, with reference to astemizole, terfenadine, loratadine, cetirizine, ebastine, mizolastine, and epinastine (Fig. 1). Special emphasis is given to consequences in terms of pharmacokinetic interactions, cardiac side-effects, and variability in clinical response. This paper also briefly discusses some other related issues that have only recently gained attention.

Pharmacokinetic properties

The pharmacokinetic properties of second-generation antihistamines have been previously discussed in some comprehensive reviews (1–5). After oral administration, second-generation H₁ antagonists are rapidly absorbed, and peak plasma concentrations ($C_{\max}$) are reached after 1–3 h. Elimination half-life varies from a few minutes (ebastine) to 20 h (astemizole). Their pharmaco-

kinetic and pharmacodynamic properties generally ensure a rapid onset of action (with the exception of astemizole, for which several days are required to achieve a satisfactory therapeutic response), and once-daily administration is recommended as optimal dosing regimen (except for terfenadine and fexofenadine, for which twice-daily dosing is recommended). Most of the second-generation antihistamines show significant renal clearance; therefore, dose adjustment may be required in patients with renal impairment. As illustrated in Table 1, plasma concentrations after recommended doses are highly variable among the second-generation H₁ antagonists. Extensive first-pass liver metabolism as well as high tissue uptake account for the very low plasma levels obtained after administration of astemizole, terfenadine, loratadine, and ebastine, which are all transformed to a pharmacologically active metabolite. Usually, the elimination half-life of the active metabolite exceeds that of the parent compound. Another common feature of these compounds is that their metabolism is mediated primarily by CYP3A4, an isoenzyme belonging to the cytochrome P-450 (CYP) superfamily (6). CYP3A4 is the most abundant CYP isoenzyme in man, accounting for 30% of total CYP in the liver and 70% in the intestine (7). Besides antihistamines, CYP3A4 can accommodate a large variety of structurally diverse exogenous and endogenous compounds. It should be noted that CYP3A4 can be inhibited or induced by a number of drugs; hence, it is implicated in many drug interactions. Substrates, inhibitors, and inducers of CYP3A4 are listed in Table 2. In contrast, cetirizine, epinastine, and fexofenadine are on the other side of the

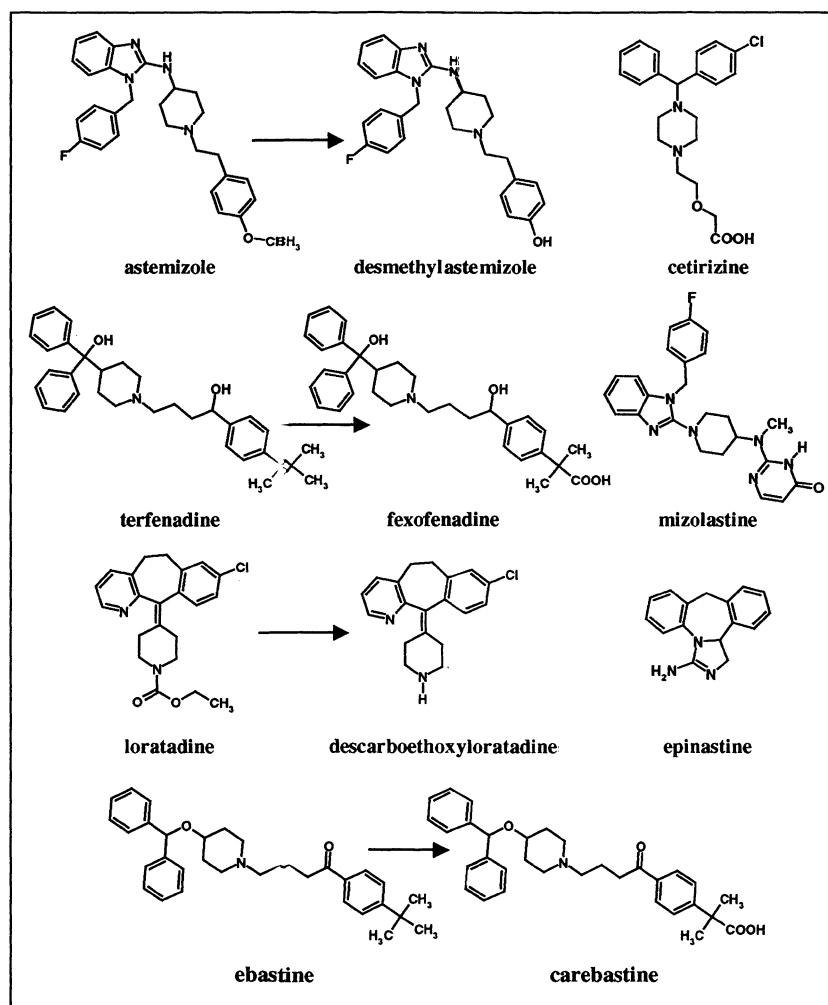


Figure 1. Representative second-generation H₁ antihistamines and their active metabolites.

metabolic hurdle, and most of the dose is eliminated as unchanged drug. Furthermore, no active metabolites have been reported for these agents.

Role of CYP3A4 in antihistamine metabolism

Astemizole undergoes a nearly complete transformation, mainly via CYP3A4, to at least 10 different metabolites (10, 11). Metabolic routes include O-demethylation, aromatic hydroxylation at the benzimidazole moiety, N-dealkylation at the piperidine nitrogen, and glucuronooconjugation. Some of these metabolites are pharmacologically active and are thought to contribute to the long-lasting activity of the drug (1, 3, 12). Terfenadine also undergoes virtually complete first-pass metabolism via CYP3A4 (13–15). The products are an inactive N-dealkylated metabolite (azacyclonol) and an active carboxylic derivative, fexofenadine. Similarly, loratadine is almost entirely eliminated as metabolic products (16). It is thought that the drug is initially hydrolyzed to form descarboethoxyloratadine, which is, in turn, further hydroxylated.

Descarboethoxyloratadine shows antihistaminic activity, and its formation is primarily mediated by CYP3A4, with some contribution by CYP2D6 (17). Ebastine is chemically related to terfenadine. Therefore, it is not surprising that ebastine is totally transformed into two major metabolites; i.e., a pharmacologically active carboxylic acid derivative (carebastine) and an inactive N-dealkylated metabolite (18, 19). CYP3A4, as well as other unidentified CYP isoforms, is involved in these reactions (20). Mizolastine is also extensively transformed. However, unlike the other compounds, mizolastine is mainly eliminated as conjugates (with only a limited contribution of CYPs), and no active metabolite has been reported (9).

CYP3A4 and drug–drug interaction

The involvement of CYP3A4 in antihistamine metabolism has been given special consideration since it has been reported that terfenadine can produce severe ventricular arrhythmia when coadministered with the CYP3A4 inhibitors erythromycin and ketoconazole

Table 1. Comparative pharmacokinetics of major second-generation H₁ antihistamines^a

	Recommended dose (mg)	C _{max} (ng/ml) ^b	Elimination t _{1/2} (h) ^b	Drug excreted unchanged (%)	Active metabolite
Astemizole	10	< 1	20–24	< 1	Desmethylastemizole
Terfenadine	60 (b.i.d.)	1	8.5	0.5	Fexofenadine
Cetirizine	10	257	7–10	> 60	None
Loratadine	10	5	12–15	20	Descarboethoxyloratadine
Ebastine	10	Not detected	Minutes	Traces	Carebastine
Epinastine	10	Not reported	Not reported	Most of dose	None
Fexofenadine	60 (b.i.d.)	209	14.4	> 85	None
Mizolastine	10	300	8–10	Traces	None

^a Adapted from references 1, 2, 3, 4, 5, 8, 9.^b Refers to parent drug.

(21–23). These compounds hinder the metabolic clearance of terfenadine, thereby inducing its accumulation, which, in turn, triggers the cardiac response. These effects are thought to be due to the potency of terfenadine to block cardiac potassium channels, leading to QT-interval prolongation and, eventually, development of torsade de pointes, a potentially fatal ventricular arrhythmia. Additional precipitating factors associated with elevated terfenadine levels include drug overdose and hepatic insufficiency. Subsequent investigations have shown that other clinical substrates and/or inhibitors of CYPs significantly impair terfenadine metabolism; e.g., itraconazole (22), troleandomycin (25), fluoxetine (26), clarithromycin (23), fluconazole (27), and zileuton (28). Some of these interactions are sufficient to induce electrocardiographic changes. The potential seriousness of these adverse events led to the withdrawal of terfenadine from the US market in 1997 after fexofenadine, the active and noncardiotoxic metabolite, became available as a safer alternative.

Table 2. Substrates, inhibitors, and inducers of CYP3A4

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

Astemizole has also been reported to induce torsade de pointes when taken in overdose (29, 30) or when coadministered with CYP inhibitors such as ketoconazole (31) or erythromycin (32). Although the process is still unclear, some astemizole metabolites might contribute to the cardiac response (33). In view of the long elimination half-life of the drug and its metabolites (up to 20 days), cardiac adverse events are expected to be difficult to terminate. These observations resulted in more restrictive labeling; more recently, the compound has been withdrawn from most markets. In line with their metabolic profile, loratadine, ebastine, and, to a lesser extent, mizolastine are sensitive to drug interactions. Plasma concentrations of loratadine are increased after coadministration with the CYP3A4 inhibitors erythromycin, ketoconazole, clarithromycin, and cimetidine (34–36). Similarly, plasma levels of ebastine and mizolastine are elevated when coadministered with erythromycin or ketoconazole (18, 37). The pharmacokinetic interactions encountered with loratadine, ebastine, and mizolastine are usually regarded as not clinically relevant since neither electrocardiographic abnormalities nor other adverse events were recorded as a result of drug accumulation (38, 39).

As a consequence of its low extent of transformation (40), cetirizine disposition is not affected by coadministration with ketoconazole (data on UCB files), erythromycin (41), azithromycin (42), or cimetidine (43). Furthermore, coadministration with erythromycin (41) or overdosage (44) is not associated with QT prolongation or adverse cardiac reactions. Absence of QT change was further confirmed in volunteers receiving cetirizine at doses up to six times the recommended daily dosage (45). Fexofenadine and epinastine also display negligible metabolism (46, 47); thus, they should not interact with CYP inhibitors. Surprisingly, it was reported that fexofenadine levels rise after concomitant administration with either ketoconazole or erythromycin (48). This interaction is likely to occur at the intestinal level, but the mechanism is not yet fully elucidated. No clinical interaction data are available for epinastine. Both fexofenadine and epinastine are considered to be free of adverse cardiac effects (48–50).

The available evidence suggests that arrhythmogenic potential is not an inherent characteristic of all second-generation antihistamines. To date, only terfenadine and astemizole have been definitely proven to engender some risk, suggesting that this is not a class effect. However, it must be borne in mind that extensive clinical experience is lacking for newer compounds. Furthermore, some studies investigating cardiac side-effects are marked by the small population size examined, and occasional contradictory findings have been reported. In addition, considering the number of drugs interfering with CYP3A4, it is anticipated that some interactions involving antihistamines are not yet cataloged. Overall, antihistamines with low CYP-dependent metabolism and no potential for drug interactions should be considered to offer a more predictable response.

Another mechanism of pharmacokinetic interaction is induction of metabolic clearance, which lowers plasma drug levels. Rifampin, a drug increasingly prescribed because of the resurgence of tuberculosis, is a potent inducer of CYP3A4 activity (51). Consequently, rifampin significantly reduces plasma levels of estradiol, a CYP3A4 substrate, and thereby compromises the clinical efficacy of oral contraceptives. Other CYP3A4-inducing agents are listed in Table 2. There is a paucity of data on the ability of CYP inducers to impair antihistamine pharmacokinetics. However, it was recently reported that thiazolidinediones, a new class of insulin-enhancing drugs, might induce terfenadine metabolism by CYP3A4 (52, 53).

CYP3A4 and food interaction

It is now well established that concomitant intake of grapefruit juice increases the plasma level of many drugs including cyclosporin, benzodiazepines, calcium channel antagonists, and HIV protease inhibitors (54). This effect relies on the ability of grapefruit juice to inhibit CYP3A4-dependent first-pass metabolism at the intestinal level. The magnitude of the interaction is highly unpredictable, as it is dependent on numerous factors (e.g., interindividual susceptibility, type and amount of grapefruit juice consumed, and timing of administration). A number of studies have demonstrated that coadministration of grapefruit juice with terfenadine may lead to an increase in drug exposure. The interaction may be associated with a significant prolongation of the QT interval (55, 56) and, presumably, some deaths (57). All these observations suggest an important contribution of the intestinal wall in the first-pass metabolism of antihistamines, as already suggested by *in vitro* studies (58). Another beverage that can inhibit antihistamine metabolism is tonic water that contains quinine. Quinine can interfere with CYP3A4 (59) and has been shown to elevate astemizole plasma concentrations, with a parallel

prolongation of the QT interval (60). Since these effects were observed at relevant dosages, this finding might be of clinical significance. It remains to be determined whether the above beverages can impair the pharmacokinetics and the tolerability of the other antihistamines that are metabolized by CYPs. The possibility of such interactions has led to a US Food and Drug Administration warning about astemizole.

CYP3A4 and interindividual variability

CYP3A4 expression is influenced by environmental factors; as a result, its activity varies considerably (>10-fold difference) among individuals (61). Although not fully investigated, CYP3A4 variability is likely to affect the efficacy and safety profile of antihistamines transformed by this isoenzyme. Honig et al. examined maximum terfenadine plasma concentration at steady state in 150 healthy volunteers (62). Terfenadine was undetectable in all but 11 subjects (concentrations of 6–14 ng/ml), demonstrating a wide interindividual variability in drug disposition. Similarly, a marked variability in the effect of ketoconazole on terfenadine pharmacokinetics and QT response has been reported (22). Loratadine is also characterized by an extremely variable disposition. In adult volunteers, the fraction of the dose eliminated unchanged ranges from less than 1% to greater than 60%, and up to nine-fold difference in total body clearance is reported (63). Interestingly, the metabolic elimination of loratadine involves both CYP3A4 and CYP2D6, another CYP isoenzyme variably expressed in the population (64). Apparently, patients with the lowest CYP activities are at risk of developing toxic concentrations of antihistamines even when using recommended doses without interfering drugs. Less is known concerning the influence of CYP variability on the therapeutic activity of antihistamines that act as prodrugs.

Antihistamines as CYP inhibitors

Over the past decade, the ability of second-generation antihistamines to elicit pharmacokinetic drug interactions has been extensively investigated. However, most of the studies have focused on the ability of CYP inhibitors to impair the disposition of antihistamines. Conversely, there is little information on the effect of antihistamines on the disposition of coadministered drugs. Recently, some selected second-generation antihistamines have been screened for their ability to inhibit CYP marker activities in human liver microsomes. The most noticeable finding was a potent inhibitory effect of loratadine on (*S*)-mephenytoin 4-hydroxylation, a CYP2C19-mediated reaction. In the same study, terfenadine, astemizole, cetirizine, and mizolastine were found to be devoid of any potent inhibitory

effect (65). In a recent paper, some classical first-generation antihistamines were reported to inhibit CYP2D6 activities *in vitro* (66). Whether these data have any clinical relevance remains to be determined.

Antihistamines and P-glycoprotein

In vitro studies have suggested that terfenadine, azelastine, and ebastine can reverse multidrug resistance by inhibiting an energy-dependent drug efflux pump, P-glycoprotein (Pgp) (67–70). In contrast, the more hydrophilic antihistamines, cetirizine, fexofenadine, and acrivastine, are devoid of such inhibitory effect. Beside cancer cells, Pgp is also present at other sites such as the blood–brain barrier, the intestinal wall, and proximal renal tubules. It is now recognized as an important factor in drug distribution and excretion, and, not surprisingly, is the source of some important pharmacokinetic interactions (71). For example, erythromycin significantly increases the bioavailability of talinolol by inhibiting its Pgp-mediated intestinal secretion (72).

Interestingly, many substrates or modulators of CYP3A4 also interact with Pgp (73). To date, no

studies have investigated whether antihistamines with affinity for CYP3A4 can produce drug–drug interactions through inhibition of Pgp.

Conclusions

The case of terfenadine and astemizole illustrates how metabolism can seriously affect the safety of a given drug. Metabolic stability is now emerging as an important distinguishing characteristic of second-generation antihistamines. This accounts for differences in drug disposition, potential for drug–drug interactions, potential for interactions with food constituents, and intersubject variability in drug response. All these aspects are not yet fully understood. In particular, some interaction mechanisms remain to be investigated. In this context, all antihistamines should be carefully evaluated for their benefit/risk profile and for pharmacovigilance data. In addition to lack of cardiotoxic potential, low metabolic clearance and absence of interaction with detoxification mechanisms should be considered major advantages when selecting a second-generation antihistamine.

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