

IN VITRO CHARACTERIZATION OF CYTOCHROME P450 2D6 INHIBITION BY CLASSIC HISTAMINE H₁ RECEPTOR ANTAGONISTS

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ABSTRACT:

Classic antihistamines, namely diphenhydramine, chlorpheniramine, clemastine, perphenazine, hydroxyzine, and tripeleminamine, share structural features with substrates and inhibitors of the polymorphic cytochrome P450 (CYP) isozyme CYP2D6. Therefore, the current study was undertaken to characterize the *in vitro* inhibition of CYP2D6 by these commonly used, histamine H₁ receptor antagonists. Microsomal incubations were performed using bufuralol as a specific CYP2D6 substrate and microsomes derived from human cells transfected with CYP2D6 cDNA. Reaction velocities were assessed in the absence and presence of antihistamines (20 μ M) at 11 substrate concentrations (1, 2.5, 5, 7.5, 10, 15, 20, 25, 50, 75, and 100 μ M), as well as at three nonsaturating substrate concentrations (2.5, 5, and 20 μ M) and three inhibitor concentrations (5, 20, and 50 μ M). In the presence of all antihistamines, the $V_{\max}$ and K_M of bufuralol 1'-hydroxylation were significantly altered, compared

with the uninhibited reaction ($p < 0.05$). Lineweaver-Burke plots suggested competitive inhibition of the reaction by diphenhydramine and mixed inhibition by all other antihistamines tested. Diphenhydramine and chlorpheniramine, with estimated K_i values of ~ 11 μ M, were the weakest inhibitors of CYP2D6 *in vitro*. Whereas tripeleminamine, promethazine, and hydroxyzine were similar in their inhibitory capacities ($K_i \sim 4$ –6 μ M), clemastine appeared to be significantly more potent, with a K_i of ~ 2 μ M. These data demonstrate that classic histamine H₁ receptor antagonists, available in over-the-counter preparations, inhibit CYP2D6 *in vitro*. Furthermore, the CYP2D6-inhibitory concentrations of these antihistamines are in the range of their expected hepatic blood concentrations, suggesting that, under specific circumstances, clinically relevant interactions between classic antihistamines and CYP2D6 substrates might occur.

The classic histamine H₁ receptor antagonists clemastine, diphenhydramine, chlorpheniramine, tripeleminamine, promethazine, and hydroxyzine were introduced into clinical practice >50 years ago and are today among the most commonly used drugs in the world (Simons and Simons, 1994). Because these compounds have excellent overall safety records, they are found in a wide variety of over-the-counter cold and allergy treatments, as well as in sleeping aids, and they are often used in combination with other drugs (Simons and Simons, 1994). Despite their widespread use over an extended period, little is known about their pharmacokinetics, particularly their interactions with specific P450¹ isozymes.

Several observations argue for an important role of the polymorphic P450 isozyme CYP2D6 in the metabolism and the interaction profiles of classic antihistamines. First, the structural criteria elaborated for the

optimal binding of diphenhydramine and its analogues to P450 (Rekka *et al.*, 1989) are very similar to the structural characteristics of many known CYP2D6 substrates and inhibitors (de Groot *et al.*, 1997). Second, a recent study demonstrated that, *in vitro*, the residual activity of bufuralol 1-hydroxylation was lowest in the presence of clemastine (5% of control activity at a concentration of 100 μ M clemastine) and highest in the presence of diphenhydramine (40% of control activity at a concentration of 100 μ M diphenhydramine) (Nakamura *et al.*, 1996). The same investigators demonstrated that promethazine and chlorpheniramine inhibited CYP2D6 activity *in vitro*, although the type of inhibition was not determined (Nakamura *et al.*, 1996). Third, and consistent with these *in vitro* data and structural considerations, a case study reported a 2-fold increase in the half-life of diphenhydramine in an elderly woman with impaired metabolism of the CYP2D6 substrate imipramine (Glassman *et al.*, 1985). Lastly, the pharmacokinetics of classic antihistamines are characterized by intersubject variability (Chiou *et al.*, 1979; Huang *et al.*, 1982) similar to that described for CYP2D6 substrates; therefore, this variability might be the result of a genetically determined lack of metabolic capacity (Alvan, 1991).

The isozyme CYP2D6 has received considerable attention because of the presence of a genetic polymorphism that divides the population into individuals with high enzyme activity (extensive metabolizers) and individuals (5–10% of the population) with low enzyme activity (poor metabolizers) (Mahgoub *et al.*, 1977). Poor metabolizers are predisposed to the accumulation of CYP2D6 substrates and drug-induced adverse effects (Lennard, 1993). Similarly, when extensive metabolizers are treated simultaneously with a substrate and a potent

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¹ Abbreviation used is: P450 or CYP, cytochrome P450.

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TABLE 1

Inhibition of bufuralol 1'-hydroxylation by classic antihistamines (means $\pm$ 95% confidence intervals)

Antihistamine	$V_{\max}$	K_M	K_i		
			Competitive	Noncompetitive	Mixed
	pmol/pmol CYP2D6/min	μM		μM	
None (control)	2.51 $\pm$ 0.25	10.0 $\pm$ 3.3			
Diphenhydramine	1.75 $\pm$ 0.18	18.6 $\pm$ 5.2	11.7 $\pm$ 2.8 ^a	49.8 $\pm$ 13.1	30.4 $\pm$ 6.6
Chlorpheniramine	1.84 $\pm$ 0.10	37.8 $\pm$ 4.7	5.4 $\pm$ 0.4	25.6 $\pm$ 6.3	10.8 $\pm$ 1.4 ^b
Clemastine	0.61 $\pm$ 0.03	32.8 $\pm$ 8.7	0.8 $\pm$ 0.1	4.8 $\pm$ 1.1	2.0 $\pm$ 0.3 ^b
Tripeleennamine	1.74 $\pm$ 0.34	54.5 $\pm$ 20.9	3.1 $\pm$ 0.4	15.8 $\pm$ 4.1	5.6 $\pm$ 0.8 ^b
Promethazine	1.05 $\pm$ 0.10	37.1 $\pm$ 7.8	1.9 $\pm$ 0.2	8.5 $\pm$ 2.3	3.8 $\pm$ 0.7 ^b
Hydroxyzine	1.01 $\pm$ 0.21	36.0 $\pm$ 7.4	1.6 $\pm$ 0.4	9.3 $\pm$ 2.2	3.9 $\pm$ 0.5 ^b

^a Competitive inhibitor, according to Lineweaver-Burke plot.^b Mixed inhibitors, according to Lineweaver-Burke plots.

inhibitor of CYP2D6, substrate accumulation occurs (Brosten *et al.*, 1987).

The objectives of the present study were to substantiate and extend previous work by determining the type of inhibition of *in vitro* CYP2D6 activity produced by the classic histamine H₁ receptor antagonists diphenhydramine, chlorpheniramine, promethazine, and clemastine. Furthermore, we intended to determine the type and extent of CYP2D6 inhibition produced by two additional, structurally related, classic antihistamines, namely tripeleennamine and hydroxyzine.

Materials and Methods

Chemicals. Clemastine fumarate, chlorpheniramine maleate, promethazine hydrochloride, tripeleennamine hydrochloride, diphenhydramine hydrochloride, hydroxyzine dihydrochloride, NADP, glucose-6-phosphate, and glucose-6-phosphate dehydrogenase were obtained from Sigma Chemical Co. (St. Louis, MO). Magnesium chloride was purchased from Anachemia Science (Ville St-Pierre, Montreal, Quebec, Canada), and ($\pm$)-bufuralol hydrochloride and 1'-hydroxybufuralol were purchased from Gentest Corp. (Woburn, MA). Other chemicals were obtained from the usual commercial sources and were of analytical grade.

Recombinant Human CYP2D6 Isozymes. Human microsomes expressing CYP2D6 protein was purchased from Gentest. This protein was derived from a human AHH-1-TK^{+/+} cell line transfected with cDNA encoding human CYP2D6-Val₃₇₄.

Microsomal Incubations. Incubations (final volume, 250 μ l) contained substrate (0–350 μ M bufuralol in 100 mM potassium phosphate buffer, pH 7.4), 10 μ l of microsomes (0.4 mg/ml), 100 μ l of a NADPH-regenerating system (7.75 mg of NADP, 7.75 mg of glucose-6-phosphate, and 36 units of glucose-6-phosphate dehydrogenase in 3.0 ml of 100 mM potassium phosphate buffer, pH 7.4), and potassium phosphate buffer (100 mM, pH 7.4). Incubation mixtures containing microsomes, substrate, and buffer were preincubated at 37°C for 10 min before the addition of the NADPH-regenerating system. The resulting mixture was incubated for 30 min at 37°C in a Dubnoff incubator (Precision Scientific, Chicago, IL), and the reaction was stopped by the addition of 25 μ l of perchloric acid (69–72%, by volume). Proteins were sedimented by centrifugation. All experiments were performed in duplicate.

Clemastine fumarate, chlorpheniramine maleate, promethazine hydrochloride, tripeleennamine hydrochloride, diphenhydramine hydrochloride, and hydroxyzine dihydrochloride were dissolved in potassium phosphate buffer (100 mM, pH 7.4). To characterize the type and extent of inhibition of CYP2D6 by antihistamines, incubation mixtures contained microsomes, buffer, cofactor, 11 concentrations of bufuralol (1–100 μ M), and a fixed concentration (20 μ M) of each antihistamine. In addition, for graphical determination of K_i values for the antihistamines, incubations were performed with three nonsaturating bufuralol concentrations (2.5, 5, and 20 μ M) and three inhibitor concentrations (5, 20, and 50 μ M). Bufuralol and its hydroxylated metabolite were analyzed by HPLC as described previously (Kronbach *et al.*, 1987).

Data Analysis. Reaction velocities were expressed in units of picomoles of 1'-hydroxybufuralol formed per picomole of CYP2D6 per minute. Velocity data for bufuralol 1'-hydroxylation in the absence and presence of antihistamines were estimated by derivative-free, iterative, nonlinear, least-squares

regression (Fig60; Biosoft, Ferguson, MO). Comparisons of the rates of formation of 1'-hydroxybufuralol at various inhibitor concentrations were accomplished graphically by using the Dixon method. In addition, K_i values were estimated by nonlinear, least-squares regression, using equations for competitive [$V = V_{\max} \cdot S / (S + K_M(1 + I/K_i))$], noncompetitive [$V = V_{\max} \cdot S / (S(1 + I/K_i) + K_M)$], or mixed [$V = V_{\max} \cdot S / (S(1 + I/\alpha K_i) + K_M(1 + I/K_i))$] inhibition. Data are expressed as means and 95% confidence intervals.

Results and Discussion

Estimated $V_{\max}$, K_M , and K_i values for bufuralol 1'-hydroxylation *in vitro* are summarized in table 1. Compared with the uninhibited reaction (control), addition of all antihistamines resulted in significant changes of $V_{\max}$ and K_M , with no overlap of the 95% confidence intervals (all $p < 0.05$, compared with control). Lineweaver-Burke plots (not shown) suggested that diphenhydramine is a competitive inhibitor and that chlorpheniramine, clemastine, tripeleennamine, promethazine, and hydroxyzine are mixed inhibitors of CYP2D6 *in vitro* (table 1). Fitting of velocity data by derivative-free, iterative, nonlinear, least-squares regression, assuming competitive or mixed inhibition, revealed that diphenhydramine and chlorpheniramine, with estimated K_i values of ~ 11 μ M, were significantly weaker inhibitors of CYP2D6 *in vitro* than were the other antihistamines tested (both $p < 0.05$). Tripeleennamine, promethazine, and hydroxyzine were similar in their inhibitory capacities ($K_i \sim 4$ –6 μ M) and were significantly more potent inhibitors than diphenhydramine and chlorpheniramine ($p < 0.05$). Of all antihistamines tested, clemastine appeared to be the most potent *in vitro* inhibitor, with a K_i of ~ 2 μ M ($p < 0.05$, compared with all other antihistamines). K_i values obtained by regression analysis corresponded to the respective K_i values obtained from Dixon plots. These results appear to be clinically relevant, because all antihistamine drugs tested undergo extensive first-pass metabolism, resulting in hepatic blood concentrations that are expected to lie in the range of the determined K_i values (table 2).

Our results are in agreement with previous reports of *in vitro* CYP2D6 inhibition by various antihistamines. K_i values reported for diphenhydramine ranged from 0.124 to 2.5 μ M, depending on the type of *in vitro* system and substrate used (Fonne-Pfister and Meyer, 1988; Hiroi *et al.*, 1995). Furthermore, K_i values for promethazine and chlorpheniramine were graphically estimated to be 13 and 20 μ M, respectively, and clemastine as well as diphenhydramine inhibited CYP2D6-mediated bufuralol 1'-hydroxylation *in vitro* (Nakamura *et al.*, 1996). The data presented by us extend previous work by including a whole series of the most commonly used classic antihistamines, by assessing not only the extent but also the type of inhibition, and by using a more objective approach of nonlinear regression analysis.

These *in vitro* data, suggesting that classic antihistamines may indeed be rather potent inhibitors of CYP2D6, are somewhat incon-

TABLE 2
Plasma tissue concentrations of classic antihistamine drugs

Antihistamine	Plasma Concentration	Plasma Concentration ^a	Tissue Concentration ^b	Expected Liver Concentration	Reference
	$\mu\text{g/ml}$	μM		μM	
Diphenhydramine HCl	0.06–0.09	0.21–0.55	Liver/blood, 10:1	2–5	Blyden <i>et al.</i> , 1986; Jones and Pounder, 1987
Chlorpheniramine maleate	0.02	0.05	Liver/plasma, 22:1	1.2	Athanikar <i>et al.</i> , 1979; Kamm <i>et al.</i> , 1969
Tripeleminamine HCl	0.11	0.36	Liver/blood, 2–7:1	0.7–2.5	Yeh <i>et al.</i> , 1986; Rao <i>et al.</i> , 1975
Clemastine fumarate	0.002–0.01	0.004–0.02			Tham <i>et al.</i> , 1978
Hydroxyzine HCl	0.073–0.08	0.16–0.17	Liver/blood, 10:1	1.7	Pong and Huang, 1974; Simons <i>et al.</i> , 1984
Promethazine HCl	0.017	0.053	Liver/blood, 43:1	2.3	Taylor and Houston, 1982; Huang <i>et al.</i> , 1970

^a Plasma concentrations after single doses used clinically.

^b Derived from distribution of ¹⁴C-labeled drug in rats for chlorpheniramine, tripeleminamine, hydroxyzine, and promethazine and derived from human autopsy specimens for diphenhydramine.

sistent with the fact that these agents are perceived as being relatively safe compounds. In fact, if drug interactions between classic antihistamines and other drugs have occurred, they have not been documented in the scientific literature. What was considered most bothersome about this class of agents was that they are not selective for histamine H₁ receptors, thus inducing dopaminergic, serotonergic, and cholinergic responses (Simons and Simons, 1994). This pharmacological nonselectivity, combined with the ability to penetrate the blood-brain barrier, leads to the development of significant adverse effects in the central nervous system. These central nervous system effects occur when the drug is administered alone and appear to be related to plasma concentrations (Carruthers *et al.*, 1978) but not to race (Spector *et al.*, 1980), gender, or age (Berlinger *et al.*, 1982).

On the other hand, after oral dosing, classic antihistamines are characterized not only by rapid and extensive distribution but also by considerable accumulation after multiple doses (Paton and Webster, 1985; Huang *et al.*, 1982). If these agents are metabolized by CYP2D6, as shown directly for promethazine (Nakamura *et al.*, 1996) and indirectly for chlorpheniramine (Yasuda *et al.*, 1995), and they inhibit the same enzyme, one might speculate that autoinhibition could occur. However, multiple-dose data are limited to a few subjects and, despite an estimated accumulation factor of 4–9 for chlorpheniramine, its elimination half-life was similar after single (two subjects) and multiple (two different subjects) doses (Huang *et al.*, 1982).

The presence of aromatic rings and alkyl substituents renders classic antihistamines very lipophilic and allows these molecules to readily traverse membranes. Thus, after oral administration, antihistamine drugs undergo extensive first-pass elimination, resulting in relatively low plasma concentrations (table 2) (Tonn *et al.*, 1996). However, hepatic blood concentrations of classic antihistamines are 7–42-fold higher than the respective plasma concentrations, based on data on radiolabeled drug distribution in animals or findings from autopsy specimens (table 2). Thus, expected human hepatic blood concentrations are in the range of the determined CYP2D6-inhibitory concentrations for all classic antihistamine drugs tested. In support of this hypothesis, we recently reported that chronic administration of diphenhydramine significantly prolonged the hemodynamic effects of metoprolol in healthy volunteers with high CYP2D6 activity, compared with those with low CYP2D6 activity (Bouayad *et al.*, 1997).

In summary, six classic antihistamines, namely diphenhydramine, chlorpheniramine, clemastine, promethazine, tripeleminamine, and hydroxyzine, inhibit CYP2D6-mediated bufuralol 1'-hydroxylation *in vitro*. Because these compounds accumulate in the liver and *K_i* values are in the range of expected antihistamine concentrations in hepatic blood, classic H₁ receptor antagonists may cause clinically relevant drug-drug interactions with cardiovascular, antidepressant, and antipsychotic CYP2D6 substrates. Thus, well-controlled studies of the

interactions of classic antihistamines with such substrates must be performed with individuals with high and low CYP2D6 activities.

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