EFFECT OF ANTIPSYCHOTIC DRUGS ON HUMAN LIVER CYTOCHROME P-450 (CYP) ISOFORMS IN VITRO: PREFERENTIAL INHIBITION OF CYP2D6

JAE-GOOK SHIN, NADIA SOUKHOVA, AND DAVID A. FLOCKHART

Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Georgetown University Medical Center, Washington

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ABSTRACT:
The ability of antipsychotic drugs to inhibit the catalytic activity of five cytochrome P-450 (CYP) isoforms was compared using in vitro human liver microsomal preparations to evaluate the relative potential of these drugs to inhibit drug metabolism. The apparent kinetic parameters for enzyme inhibition were determined by nonlinear regression analysis of the data. All antipsychotic drugs tested competitively inhibited dextromethorphan O-demethylation, a selective marker for CYP2D6, in a concentration-dependent manner. Thioridazine and perphenazine were the most potent, with IC50 values (2.7 and 1.5 μM) that were comparable to that of quinidine (0.52 μM). The estimated Ki values for CYP2D6 catalyzing dextromethorphan formation were ranked in the following order: perphenazine (0.8 μM), thioridazine (1.4 μM), chlorpromazine (6.4 μM), haloperidol (7.2 μM), fluphenazine (9.4 μM), risperidone (21.9 μM), clozapine (39.0 μM), and cis-thiothixene (65.0 μM). No remarkable inhibition of other CYP isoforms was observed except for moderate inhibition of CYP1A2-catalyzed phenacetin O-deethylataion by fluphenazine (Ki = 40.2 μM) and perphenazine (Ki = 65.1 μM). The estimated Ki values for the inhibition of CYP2C9, 2C19, and 3A4 were >300 μM in almost all antipsychotics tested. These results suggest that antipsychotic drugs exhibit a striking selectivity for CYP2D6 compared with other CYP isoforms. This may reflect a remarkable commonality of structure between the therapeutic targets for these drugs, the transporters, and metabolic enzymes that distribute and eliminate them. Clinically, coadministration of these medicines with drugs that are primarily metabolized by CYP2D6 may result in significant drug interactions.
specific substrates of CYP1A2, CYP2D6, CYP2C9, CYP2C19, and CYP3A using human liver microsomes (HL) in vitro.

Materials and Methods

Chemicals. Chlorpromazine, perphenazine, fluphenazine, thioridazine, cis-thiothixene, haloperidol, clozapine, phenacetin, acetaminophen, dextromethorphan hydrobromide, tolbutamide, quinidine sulfate, glucose 6-phosphate (G-6-P), glucose 6-phosphate dehydrogenase (G-6-PDH), β-nicotinamide adenine dinucleotide phosphate, and EDTA were purchased from Sigma Chemical Co. (St. Louis, MO). Risperidone was obtained from Research Diagnostics, Inc. (Flanders, NJ). 4-Methylhydroxylumbutanide was purchased from Ultrafine Chemicals (Manchester, England) and levalloirphen from U.S.P.C. (Rockville, MD). Dextorotraphur turrate and 3-methoxymorphinophenylacetic acid were obtained from Hoffman-La Roche Inc. (Nutley, NJ). Omeprazole and 5-hydroxyomeprazole were generous gifts from Dr. Tommy Anderson (Clinical Pharmacology, Astra Hassle AB, Mölndal, Sweden). N-(4-hydroxyphenyl)butanamide was kindly provided by Dr. John Strong (Division of Clinical Pharmacology, Center for Drug Evaluation and Research, United States Food and Drug Administration, Rockville, MD). All other chemicals and reagents used were of the highest commercially available quality.

HL Human liver tissue (n = 11), medically unsuitable for liver transplantation, were acquired under the auspices of the Washington Regional Transplant Consortium (Washington, DC) and frozen at −80°C within 3 h of the cross-clamp time. HL were prepared as described previously (Ko et al., 1997) and protein concentrations were determined by the Bradford method of Pollard et al. (1978). The microsomal pellets were resuspended to a protein concentration, were acquired under the auspices of the Washington Regional Transplant Consortium (Washington, DC) and frozen at −80°C within 3 h of the cross-clamp time. HL were prepared as described previously (Ko et al., 1997) and protein concentrations were determined by the Bradford method of Pollard et al. (1978). The microsomal preparations were mixed together with others using equal volumes of each preparation used (mixed human liver, MHL). Microsomal suspensions were stored at −80°C and thawed before study.

Inhibition Studies. The effects of antipsychotic drugs on the metabolism of five different CYP isomeric–specific substrates were studied: phenacetin O-deethylation for CYP1A2 (Tassaneeyakul et al., 1993), dextromethorphan O-demethylation for CYP2D6 (Broy et al., 1989), tolbutamide 4-methylhydroxylation for CYP2C9 (Relling et al., 1990), omeprazole 5-hydroxylation (Chiba et al., 1993; Balian et al., 1995; Ko et al., 1997), and dextromethorphan N-demethylation for CYP3A (Gorski et al., 1994).

In all experiments, perphenazine, thioridazine, cis-thiothixene, haloperidol, clozapine, and risperidone were dissolved and diluted serially in ethanol. For the incubation of these antipsychotic drugs, ethanol was removed by evaporating to dryness in the 1.5-ml microfuge tube using a Speedvac SC110 model RH40–12 (Savan Instruments Inc., Farmingdale, NY) and reconstituted in phosphate buffer. Chlorpromazine and fluphenazine were dissolved in ethanol and serially diluted with distilled water. The final concentration of antipsychotic drugs tested ranged from 1 to 100 μM and that of ethanol was less than 0.1% in 250 μl of reaction volume. The reaction mixtures were prewarmed at 37°C for 5 min before adding microsomes, then incubated for 30 or 60 min for the measurement of different CYP isomeric activities. The incubation time and amount of microsomes were determined to be in the linear range for metabolism formation rate, which was expressed as the quantity of metabolite formed per unit of protein concentration and time.

The CYP1A2-catalyzed O-deethylation of phenacetin (Tassaneeyakul et al., 1993) was measured by a minor modification of the method described by Ko et al. (1997). The incubation mixtures (final volume, 250 μl) contained NADPH-regenerating system (1.3 mM β-nicotinamide adenine dinucleotide phosphate, 3.3 mM G-6-P, 3.3 mM MgCl₂, and 1 U/ml G-6-PDH) and phenacetin (25–150 μM) with or without antipsychotic drug (concentration 1–100 μM) in 0.1 M phosphate buffer (pH 7.4). Reactions were started by adding microsomes (HL-7, -14, and -G, final concentration 0.25 mg/ml), incubated at 37°C for 30 min, and terminated by placing the samples on ice and adding 1.0 ml of acetonitrile with 2 μg of internal standard, N-(4-hydroxyphenyl)butanamide. The assay of acetonaminophen and phenacetin in reaction mixtures were carried out as described previously (Ko et al., 1997). The enzyme activity was determined by acetaminophen formation rate from phenacetin and was expressed as the quantity of acetaminophen formed per unit of protein concentration and time.

The CYP2D6- and 3A-catalyzed dextromethorphan O- and N-demethyl-

antation were evaluated by measurement of dextromethorphan and 3-methoxymorphi-

nan formed, respectively (Broly et al., 1989; Gorski et al., 1994; von Molke et al., 1998). Thirty-minute incubations of dextromethorphan (10–75 μM for O-demethylation and 100–750 μM for N-demethylation), NADPH-regenerating system, and HL-10, -29, and -D for CYP2D6, and HL-10 and -B for CYP3A, final concentration 0.25 mg/ml, were performed for 30 min without or with the addition of antipsychotic drugs tested (1–100 μM) or quinidine (0.01–10 μM) as a positive control. To evaluate the possible contribution of metabolism to CYP2D6 inhibition, mixtures of NADPH-regenerating system and antipsychotic drugs (25 μM) with HL were preincubated for 20 min. After this, dextromethorphan (25 μM) was added to the reaction mixture and incubated at 37°C for a further 30 min to measure dextromethorphan formation rate. The HPLC assay with fluorescence detector was done as described previously (Ko et al., 1997).

The CYP2C9-catalyzed 4-methylhydroxylation of tolbutamide (Relling et al., 1990) was measured from 1-h incubations of tolbutamide (25–200 μM) without or with an antipsychotic drug (concentration 1–100 μM), NADPH-regenerating system, and HL-29 and -B (final concentration 0.5 mg/ml) in 250 μl of final reaction mixture. The enzymatic reaction was terminated by adding 1 ml of ice-cold ethyl alcohol, 15 μl of 1 N HCl and 25 μl of 0.01 mg/ml of chlorpropamide as an internal standard. Tolbutamide, 4-hydroxytolbutamide, and chlorpropamide were extracted with vigorous shaking on the vortex mixer for 10 min. After discarding the supernatant from centrifugation, the remaining organic phase was dried in the Speedvac (Savan Instruments Inc.) and reconstituted with 100 μl of HPLC mobile phase consisting of 35% acetonitrile in 0.022% H₃PO₄ at pH 2.65 adjusted with triethyamine. Tolbutamide and 4-hydroxytolbutamide were separated on an Alltech Spherisorb DDS (250 × 4.6 mm, 5 μM) with Waters Novapak C₁₈ guard column at a flow rate of 0.8 ml/min and detected by Waters 490 UV detector set at 240 nm wavelength.

CYP2C19 activity was assayed by measuring 5-hydroxyomeprazole formation (Chiba et al., 1993) from 1-h incubations of omeprazole (25–150 μM) without and with an antipsychotic drug (1–100 μM), NADPH-regenerating system, and HL-29 and -B (final concentration 0.5 mg/ml). The reaction was terminated by adding 100 μl of ice-cold acetonitrile with 40 μl of 0.25 mg/ml phenacetin, the internal standard. After centrifugation at 14,000 rpm in a microfuge for 5 min, 150 μl of the supernatant was injected into the HPLC system. Omeprazole, 5-hydroxyomeprazole, and phenacetin were separated on a Microsorb C₁₈ column (150 × 4.6 mm) with a flow rate of 1.2 ml/min in a mobile phase of 40% methanol with 1.4% triethylamine (pH 7.4 adjusted with phosphoric acid). Chromatograms were obtained from a Waters 484 UV detector with the wavelength set at 302 nm.

Data Analysis. The apparent kinetic parameters for CYP isoform-specific metabolite formation (Vₘₐₓ, Kₘ) and enzyme inhibition by antipsychotic drugs (IC₅₀, Kᵢ) were determined by nonlinear least square regression analysis using WinNonlin Version 1.5 (Scientific Consulting Inc., Apex, NC). These data were fitted to different models of enzyme inhibition: pure and partial competitive inhibition, noncompetitive inhibition, mixed type inhibition, and uncompetitive inhibition (Segel, 1975). The type of inhibition was determined by following several criteria: visual inspection of Lineweaver-Burk double reciprocal plots, Dixon plots, and secondary plots of Lineweaver-Burk plot versus antipsychotic concentrations; the size of the sum of squares of the residuals, Akaike Information Criteria and Schwartz Criteria values, the S.E. and 95% confidence interval of the parameter estimates, and the random distribution of the residuals from the nonlinear regression analysis.

To compare the relative inhibitory potentials of antipsychotic drugs tested, the ratio |I|/Kᵢ as an index of the potency of inhibition relative to the therapeutically effective concentration and predicted percent in vivo inhibition by antipsychotic drugs were calculated using the following relationships:

for competitive inhibition, % inhibition = \left[\frac{|I|}{1 + \frac{1}{\alpha} \cdot \left(\frac{S}{Kᵢ} + Kᵢ\right)}\right] \times 100

for partial competitive inhibition, % inhibition = \left[\frac{|I|\left(1 - \frac{1}{\alpha}\right)}{1 + \frac{S}{\alpha \cdot Kᵢ} + Kᵢ\left(1 + \frac{S}{Kᵢ}\right)}\right] \times 100

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the other drugs tested, with mean IC50 s estimated to be 136.6, 92.2, and 39.1 M, respectively (Fig. 2). Compared with Km value because the therapeutic range of plasma drug concentration is usually much less than its Km value. The concentrations of antipsychotic drugs used in these calculations were the median values of the therapeutic range of plasma drug concentrations (Javaid, 1994; Hardman et al., 1995) and 100-fold concentrations of these median values with the assumption of high accumulation of all antipsychotics in liver tissue (Dinovo et al., 1978; Forsman et al., 1981).

Results

The apparent metabolic constants (Km, Vmax) of HL used in these experiments were calculated from the nonlinear regression of the data on specific CYP isoform-catalyzed formation of metabolites (Table 1). Compared with Km values, Vmax values of the metabolic reactions tested showed large variations between different livers.

All antipsychotic drugs preferentially inhibited CYP2D6-catalyzed dextromethorphan O-demethylation compared with other CYP isoform-catalyzed reactions (Fig. 1). Among the antipsychotic drugs tested, thioridazine and perphenazine were the most potent inhibitors and decreased the dextromethoran formation rate to 26.3 and 19.7% of control activity at 10 μM, and 11.4 and 10.7% of control activity at 25 μM, respectively. The inhibitory potency of these drugs on dextromethorphan O-demethylation was comparable to the inhibitory effect of 10 to 25 μM quinidine (Fig. 2). The estimated mean IC50 values for thioridazine and perphenazine were 2.7 ± 0.5 and 1.5 ± 0.3 μM, respectively. The IC50 of quinidine, a potent CYP2D6 inhibitor, was estimated to be 0.52 ± 0.2 μM under these conditions. The estimated IC50s of chlorpromazine, fluphenazine, and haloperidol were 9.7, 16.3, and 14.4 μM, respectively (Fig. 2).

All antipsychotic drugs inhibited CYP2D6 activity, obtained from two or three different liver microsomal preparations.

The double reciprocal plots, Dixon plots, and secondary plots of slope of double reciprocal plots versus inhibitor concentration of chlorpromazine, fluphenazine, cis-thiothixene, clozapine, and risperidone showed the same type of inhibition. Representative plots for chlorpromazine are presented in Fig. 3. All these plots indicated that chlorpromazine, fluphenazine, cis-thiothixene, clozapine, and risperidone competitively inhibited dextromethorphan O-demethylation. In addition, the inhibitory effects of these antipsychotic drugs were best fitted to a pure competitive inhibition model by nonlinear regression analysis using WinNonlin.

The double reciprocal plot, Dixon plot, and secondary plot versus antipsychotic concentration showed hyperbolic curves when thioridazine, perphenazine, and haloperidol were incubated as inhibitors of dextromethorphan O-demethylation. The plots for perphenazine are shown in Fig. 4. Partial competitive inhibition was the best model to describe these data.
The $K_i$ values of antipsychotic drugs were obtained from nonlinear regression using the appropriate pure or partial competitive inhibition models (Table 2). Perphenazine and thioridazine showed the lowest $K_i$ values at around 1 µM. Mean $K_i$ values of chlorpromazine, haloperidol, and fluphenazine were 6.3, 7.2, and 9.4 µM, respectively. The drug with the highest $K_i$ was cis-thiothixene (65 µM). Of note, the atypical antipsychotics clozapine and risperidone, with estimated $K_i$ values of 39 and 21.9 µM, were weaker inhibitors than the conventional antipsychotic drugs tested.

A 20-min preincubation increased the inhibition by cis-thiothixene, haloperidol, and clozapine on CYP2D6-catalyzed dextromethorphan O-demethylation by 20% over control without preincubation (Fig. 5). No significant increase of inhibition was observed from the preincubation of thioridazine, perphenazine, fluphenazine, or risperidone.

The antipsychotic drugs had no remarkable inhibitory effect on CYP1A2-, CYP2C9-, CYP2C19-, or CYP3A-catalyzed reactions with the exception of moderate inhibition by fluphenazine and perphenazine of CYP1A2-catalyzed phenacetin O-deethylation (Fig. 1B). A competitive inhibition model was best-fitted to the data for inhibition by fluphenazine and perphenazine of CYP1A2-catalyzed phenacetin O-deethylation. The estimated mean $K_i$ values were 40.2 µM for fluphenazine and 65.1 µM for perphenazine.

Thioridazine, fluphenazine, and clozapine showed very weak inhibition of CYP2C9-catalyzed tolbutamide 4-methylhydroxylation, with estimated mean $K_i$ values of 174.6, 350, and 327.3 µM, respectively (Fig. 1C). The CYP2C19-catalyzed formation of 5-hydroxymeprazole and CYP3A-catalyzed formation of 3-methoxymorphinan from dextromethorphan were not inhibited by any of the antipsychotics tested (Fig. 1, D and E). The $K_i$ values were estimated to be >300 µM from the best-fitted competitive or noncompetitive inhibition models.

**Discussion**

In this study, all of the antipsychotic drugs tested strongly and competitively inhibited the CYP2D6-catalyzed O-demethylation of dextromethorphan, but they had no notable effect on the other CYP isoforms evaluated. It was interesting that clozapine, which is metabolized mainly by CYP1A2 and CYP3A4 (Eiermann et al., 1997), also showed competitive inhibition of CYP2D6-catalyzed dextromethorphan O-demethylation with a $K_i$ of 39.0 µM, but no remarkable inhibition of CYP1A2- and CYP3A-catalyzed enzyme reactions. There is a precedent for inhibition of CYP2D6 by drugs whose metabolism is not catalyzed by it. Quinidine and halofantrine compete for the substrate-binding site of CYP2D6 but are not metabolized by it (Otton et al., 1988; Halliday et al., 1995). Pimozide, an antipsychotic drug, is another example. Pimozide is metabolized by CYP3A and CYP1A2 and not by CYP2D6, but it does inhibit CYP2D6 (Desta et al., 1998). From the data obtained from this study, it seems clear that almost all antipsychotic drugs have the potential to inhibit CYP2D6. Many of these drugs (chlorpromazine, fluphenazine, perphenazine, haloperidol, thioridazine, risperidone, trifluperidol, and zuclopenthixol) are also metabolized by this CYP isoform (Taylor and Lader, 1996; Michalets, 1998). It follows that antipsychotic drugs may develop pharmacokinetic drug interactions with coadministered antipsychotics and antidepressants (amitriptyline, imipramine, nor triptyline, desipramine, clomipramine, maprotiline, trazodone, paroxetine,
and fluoxetine) that are not only metabolized by CYP2D6 but also inhibit it (Taylor and Lader, 1996; Meyer et al., 1996; Sproule et al., 1997). These interactions may cause serious adverse effects due to the increase in plasma concentrations of drugs that have low therapeutic indices (Goff and Baldessarini, 1993; Michalets, 1998) if these data are confirmed in clinical studies.

Available data on the inhibition of drug metabolism in vitro by antipsychotics are confined to studies of a small number of drugs, including thioridazine, chlorpromazine, olanzapine, and clozapine (Von Bahr et al., 1985; Murray and Reidy, 1989; Ring et al., 1996; Ereshefsky, 1996). Our data provide a comprehensive assessment of the ability of these drugs to interact with CYP isoforms important to drug metabolism in a single study, using consistent conditions. Von Bahr et al. (1985) reported the estimated $K_i$ values of thioridazine and chlorpromazine for CYP2D6-catalyzed desmethylimipramine 2-hydroxylation to be 0.75 and 6 $\mu$M, respectively. Clozapine was reported to inhibit CYP2D6-catalyzed bufuralol 1′-hydroxylation with a $K_i$ of 19 $\mu$M and CYP2C19-catalyzed 4-hydroxy S-mephénytoïn formation with a $K_i$ of 69 $\mu$M (Ring et al., 1996). In our study, clozapine competitively inhibited CYP2D6-catalyzed dextromethorphan O-demethylation with a $K_i$ of 39 $\mu$M and noncompetitively inhibited CYP2C19-catalyzed omeprazole S-hydroxylation with a $K_i$ of 316 $\mu$M, respectively. The relative inhibitory potency of antipsychotics reported by Ring et al. (1996) seems similar to ours even though the estimated $K_i$ values of the antipsychotics are different.

### Table 2

<table>
<thead>
<tr>
<th>Antipsychotic Drug</th>
<th>Type of Inhibition</th>
<th>$K_i$ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perphenazine$^b$</td>
<td>Partial Competitive</td>
<td>0.8 ± 0.4$^a$</td>
</tr>
<tr>
<td>Thioridazine$^a$</td>
<td>Partial Competitive</td>
<td>1.4 ± 0.8</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Competitive</td>
<td>6.3 ± 3.8</td>
</tr>
<tr>
<td>Haloperidone$^b$</td>
<td>Partial Competitive</td>
<td>7.2 ± 4.9</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Competitive</td>
<td>9.4 ± 1.5</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Competitive</td>
<td>21.9 ± 1.7</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Competitive</td>
<td>39.0 ± 14.4</td>
</tr>
<tr>
<td>cis-Fluothiexone</td>
<td>Competitive</td>
<td>65.0 ± 42.7</td>
</tr>
</tbody>
</table>

$^a$ Each value indicates mean ± S.D. obtained from three different livers.

$^b$ Mean (S.D.) of $K_i$ values of the remaining drugs were as follows: thioridazine, 72.5 ± 28.9; haloperidol, 5.7 ± 1.9.

Differences in the $K_i$ values may be caused partly by differences in the substrates used (Boobis, 1995). To estimate the clinical relevance of CYP2D6 inhibition by antipsychotics, we compared the expected relative inhibitory potency in vivo to the known therapeutic plasma concentrations of antipsychotic drugs (Javaid, 1994; Hardman et al., 1995). For this purpose, we calculated the potency of inhibition relative to the therapeutic concentration ([I]/$K_i$), a measure of specificity as well as potency of an inhibitor (Boobis, 1995) and the predicted percent inhibition as described (Table 3). Thioridazine showed the highest [I]/$K_i$, with a value of 1.46. Those of chlorpromazine and clozapine were 0.06 and 0.04, respectively. The [I]/$K_i$ of the remaining drugs were as follows: perphenazine (0.0069) > haloperidol (0.0039) > risperidone.

### Figure 4

Inhibitory effect of perphenazine on CYP2D6-catalyzed dextromethorphan O-demethylation in HL.

A, representative double reciprocal plot obtained from 30-min incubation of human liver microsomes (HL-29, 0.25 mg/ml) with an NADPH regenerating system and dextromethorphan (10–25 $\mu$M) in the absence (○) or presence of 1 (▲), 10 (▲), 25 (▲), 50 (+), 75 (●), or 100 (+) $\mu$M perphenazine. B, hyperbolic Dixon plot obtained from 30-min incubation with 10 (▲), 25 (▲), 50 (▲), or 75 (●) $\mu$M of dextromethorphan in the absence or presence of perphenazine (1–100 $\mu$M). C, hyperbolic secondary plot of slopes taken from double reciprocal plots versus perphenazine concentration. Double reciprocal plot, Dixon, and secondary plots of thioridazine and haloperidol are similar to those of perphenazine. Each data point represents an average of duplicates.

### Figure 5

Effect of preincubation on inhibition of CYP2D6-catalyzed dextromethorphan O-demethylation by antipsychotic drugs in human liver microsomal incubations.

Dextromethorphan O-demethylation was measured with or without 20-min preincubation of antipsychotics with preparation HL-10. Each value indicates average of duplicate determinations. Abbreviations are: PPZ, perphenazine; TRD, thioridazine; CPZ, chlorpromazine; HAL, haloperidol; FPZ, fluphenazine; RIS, risperidone; CZP, clozapine; cTH, cis-thiothixene.

Differences in the $K_i$ values may be caused partly by differences in the substrates used (Boobis, 1995). To estimate the clinical relevance of CYP2D6 inhibition by antipsychotics, we compared the expected relative inhibitory potency in vivo to the known therapeutic plasma concentrations of antipsychotic drugs (Javaid, 1994; Hardman et al., 1995). For this purpose, we calculated the potency of inhibition relative to the therapeutic concentration ([I]/$K_i$), a measure of specificity as well as potency of an inhibitor (Boobis, 1995) and the predicted percent inhibition as described (Table 3). Thioridazine showed the highest [I]/$K_i$, with a value of 1.46. Those of chlorpromazine and clozapine were 0.06 and 0.04, respectively. The [I]/$K_i$ of the remaining drugs were as follows: perphenazine (0.0069) > haloperidol (0.0039) > risperidone.
have a common structure that allows interaction with CYP2D6. Strobl et al. (1993) described a pharmacophore model for CYP2D6 in which at least one aromatic ring and a tertiary nitrogen atom that is protonated under physiologic condition are required. Most antipsychotic drugs tested do have an aromatic ring and tertiary nitrogen. Secondly, it is possible that antipsychotics inhibit CYP2D6 activity in the brain and that this may contribute to their therapeutic effects. CYP2D6 has been reported to be expressed in human brain and its pharmacological and immunological characteristics are similar to those of CYP2D6 from bovine and human liver tissues (Niznik et al., 1990; Gilham et al., 1997). Thirdly, the considerable evidence of structural and functional homogeneity between CYP2D6 and the dopamine transporter supports the concept that there may be a similarity between the therapeutic target of these drugs and substrates for CYP2D6 (Tyndale et al., 1991; Hiroi et al., 1997). This link appears analogous to the noted similarities between substrates of CYP3A4 and β-glycoprotein (Zhang et al., 1998; Fischer et al., 1998).

In conclusion, we have conducted a comprehensive evaluation of the effects of eight antipsychotic drugs on five CYP isoforms across a wide range of substrate and antipsychotic concentrations using in vitro human liver microsomal preparations. All the antipsychotics we tested inhibited CYP2D6, but showed no notable inhibition of CYP1A2, CYP2C9, CYP2C19, or CYP3A. These findings suggest that all antipsychotic drugs have the potential to cause pharmacokinetic drug interactions with drugs that are metabolized by CYP2D6, but it is equally important to note that they are unlikely to cause significant pharmacokinetic interactions with drugs that are primarily metabolized by other CYP isoforms. Some antipsychotics are sufficiently selective so that they may be able to serve as selective CYP2D6 inhibitors. Lastly, our data suggest that all antipsychotics have a common structure that allows binding to CYP2D6.

References


<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Concentration [µM]</th>
<th>Inhibitory Potency</th>
<th>Predicted % Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioridazine</td>
<td>2.05</td>
<td>1.46±3</td>
<td>56.27</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>0.345</td>
<td>0.0547</td>
<td>4.74</td>
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<tr>
<td>Clozapine</td>
<td>1.377</td>
<td>0.0353</td>
<td>3.11</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>0.005</td>
<td>0.0069</td>
<td>0.58</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.028</td>
<td>0.0039</td>
<td>0.34</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.015</td>
<td>0.0007</td>
<td>0.06</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0.00024</td>
<td>0.0003</td>
<td>0.02</td>
</tr>
<tr>
<td>cis-Thioxetine</td>
<td>0.019</td>
<td>0.0003</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Median values of the reference plasma concentration range (Hardman et al., 1995; Javid, 1994).

* Inhibitory potency = [1 - (1 + [S]/[K])]/[1 - (1 + [S]/[K])], where [S] is the substrate concentration and [K] is the MIC.

(0.0007) > fluoxetine = cis-thioxetine (0.0003). The predicted percent inhibition by each antipsychotic drug tested, calculated using these [K] values, is presented in Table 3.