

Psychotropic Medications Metabolized by Cytochromes P450 (CYP) 2D6 Enzyme and Relevant Drug Interactions

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Abstract

Psychotropic medications metabolized by cytochromes P450 (CYP) 2D6 are reviewed, and the possible relevance of this metabolism to drug-drug interactions is discussed. CYP2D6 is a member of the cytochrome P450 super family and it plays a primary role in the metabolism of more than 70 substrate medications, belonging to classes such as antidepressants, antipsychotics, mood stabilizers, antiarthemics, beta blockers antiemetics, opioid and Sedative/hypnotics. It is responsible for the metabolism of about 25% of the commonly prescribed drugs. CYP2D6 Primarily metabolizes four of the typical antipsychotic medications, such as haloperidol, chlorpromazine, thioridazine and perphenazine, and risperidone from second generation antipsychotics. Nortriptyline, paroxetine, fluoxetine, venlafaxine and desipramine are antidepressants which are primarily metabolized by CYP2D6. Propranolol, metoprolol, timolol and alperolol are among the common beta blockers which are primarily metabolized by CYP2D6.

Drugs which are metabolized by CYP2D6 may inhibit or induce the action of the enzyme. Drugs that inhibit CYP2D6 will predictably increase the plasma concentrations of the medications or decrease in clearance of substrates. Drugs such as bupropion, Fluoxetine, Paroxetine, norethindrone Citalopram, Escitalopram, Sertraline, Fluvoxamine, Nefazodone, Venlafaxine, clomipramine, cocaine, quinidine, and ranitidine are inhibitors of CYP2D6 enzyme.

Unlike CYP1A2, CYP2C9, CYP2C19, CYP3A4 and CYP3A5 enzymes which together with CYP2D6 metabolizes 90 percent of drugs CYP2D6 has no significant inducers.

Keywords: Cytochromes P450 (CYP) 2D6; Antipsychotics; Tricyclic antidepressants; Selective serotonin reuptake inhibitors; Beta blockers; Polymorphism; Antiarythemics

Introduction

Cytochromes P450 (CYPs) is an enzyme which metabolize the widest range of drugs, such as beta blockers, antidepressants, and opioids. They are found mainly in liver, small intestine, lungs, kidneys, placenta and Consists of more than 50 isoforms.

Cytochromes P450 (CYPs) are major source of catalytic activity for drug oxidation [1-3].

CYP2D6 is a member of the cytochrome P450 super family. It plays a primary role in the metabolism of more than 70 substrate medications, belonging to classes such as antidepressants, antipsychotics, mood stabilizers, antiarthemics, beta blockers antiemetics, opioid and Sedative/hypnotics [4-6]. It is a member of the cytochrome P450 super family, is responsible for the metabolism of about 25% of the commonly prescribed drugs [2,4-8]. It is located on chromosome 22 and consists of 4382 nucleotides. CYP2D6 codes for an enzyme that is composed of 497 amino acids.

CYP2D6 enzyme polymorphism is responsible for observed variations in drug response among patients of differing ethnic origins. Genetic variability (polymorphism) in these enzymes may influence a patient's response to commonly prescribed drug classes, including antipsychotics, beta blockers and antidepressants [4-6]. Due to considerable genetic variability (polymorphism) of CYP2D6 enzyme, drug that are metabolized by CYP2D6 (CYP2D6 substrates), certain individuals will eliminate these drugs quickly (ultrarapid metabolizers) while others slowly (poor metabolizers). If a drug is metabolized too quickly, it may decrease the drug's efficacy while if the drug is metabolized too slowly, toxicity may result [9-11]. Hence the dose of the drug may have to be adjusted to take into account of the speed at which it is metabolized by CYP2D6.

As well as in the liver, CYP2D6 is expressed in the brain where it probably plays a significant role in the metabolism of endogenous substances and neurotransmitters such as dopamine. Neuroleptic malignant syndrome (NMS) has been investigated in the Japanese population in association with CYP2D6, and it was confirmed that carriers of CYP2D6*5 have a higher risk of developing NMS [12].

CYP2D6 is primarily expressed in the liver. It is also highly expressed in areas of the CNS, including the substantia nigra. CYP2D6 is a gene with nine exons located in the long arm of chromosome 22 in region 22q13 and is highly polymorphic. Currently, about 90 mutations have been described and some of them have up to 13 subtypes [13]. CYP2D6 plays a significant role in metabolic transformation of chlorpromazine, haloperidol, perphenazine and thioridazine (Table 1) [1,12-15]. Unlike CYP1A2, there are no significant inducers of CYP2D6 activity.

Psychotropic Medications Metabolized by CYP2D6

Antipsychotic medications metabolized by CYP2D6

Primarily metabolizes four of the typical antipsychotic medications, such as haloperidol, chlorpromazine, thioridazine and perphenazine, and risperidone from second generation antipsychotics. It has substantial involvement in the metabolism of two second generation antipsychotics, aripiprazole and olanzapine [16-18].

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Group of drugs	Drug name
Antidepressants (tricyclics)	Amitriptyline, desipramine, Imiramine, Doxepine
Antidepressants (SSRIs)	Fluoxetine, Paroxetine
Antidepressants (others)	Duloxetine, Venlafaxine, nortriptyline, Mirtazapine, trazodone.
Antipsychotics (first generations)	Chlorpromazine, thioridazine, perphenazine, haloperidol
Beta-blockers	Propranolol, metoprolol, timolol, alperolol

Table 1: Common psychotropic medications metabolized by CYP2D6.

Risperidone acts as a mild to moderate 2D6 inhibitor and haloperidol is a potent 2D6 inhibitor.

Antidepressant medications metabolized by CYP2D6

CYP2D6 primarily metabolizes nortriptyline, paroxetine, fluoxetine, venlafaxine and desipramine. It substantially metabolizes mirtazapine, imipramine, amitriptyline, doxepin, duloxetine and trazodone [19-23]. Fluoxetine and paroxetine are potent inhibitors of CYP2D6 and Sertraline inhibits 2D6 in a dose-dependent manner. At doses under 100 mg/day, sertraline may only mildly inhibit 2D6. At doses above 150 mg/day, 2D6 inhibition may become moderate to potent [19-23].

Duloxetine is a moderate inhibitor of 2D6 and Mirtazapine has no significant inhibitory or inductive capabilities [4].

Mood stabilizer medications metabolized CYP2D6

Mood stabilizers including carbamaepine, valproate, lamotrigine and topiramate are not metabolized by CYP2D6 [14,15]. Lithium is mood stabilizers which are purely renally excreted, with no hepatic metabolic component. It lacks any inhibitory or inductive capabilities.

Beta blockers metabolized by CYP2D6

CYP2D6 is also involved in metabolism of beta blockers. Propranolol, metoprolol, timolol, and alperolol are among the common beta blockers which are primarily metabolized by CYP2D6 [19-23].

Drug Interactions Involving CYP2D6 Enzyme

Antipsychotic medications and interaction with other drugs

Risperidone is group of second generation antipsychotics which is primarily metabolized by CYP2D6. Because the cytochrome P450 (CYP) 2D6 mitochondrial system is involved in the metabolism of risperidone, ethnic differences and interactions with drugs that inhibit or stimulate this system will affect risperidone plasma concentrations [16-18]. Risperidone's metabolism can also be affected by drugs that are inhibitors of CYP2D6 such as paroxetine fluoxetine, quinidine or inducers of the 2D6 enzyme such as carbamazepine, phenytoin, rifampin phenobarbital. Medications that inhibit the 2D6 enzyme increase plasma levels of risperidone and decrease the rate of conversion to 9-OH-risperidone. Fluoxetine and paroxetine (strong inhibitors of 2D6) raised plasma levels of risperidone by 2.5 times and 3.9 times, respectively [19-23]. Co-administration of risperidone, which weakly inhibits CYP 2D6 with clozapine may increase the serum concentrations clozapine [4].

First generation antipsychotics such as, haloperidol, perphenazine, thioridazine, and chlorpromazine are primarily metabolized by CYP 2D6. Selective serotonin Reuptake Inhibitor (SSRI) particularly fluoxetine and paroxetin are potent inhibitors of CYP 2D6 enzyme and co-administration of this drugs with first generation antipsychotics metabolized by CYP 2D6 will increase the serum levels of antipsychotics. This may result in an increase in a worsening of extra pyramidal side

effects (EPS) [19-23]. Co-administration of other CYP 2D6 substrates including heterocyclic antidepressants, beta-blockers, and cimetidine with first generation antipsychotics may also increase antipsychotic plasma concentrations [24-34].

Antidepressant medications and interaction with other drugs

Selective serotonin Reuptake Inhibitor (SSRI) such as Fluoxetine, paroxetine, sertraline, and citalopram, inhibits the CYP 2D6 isozyme. Co-administration Selective serotonin Reuptake Inhibitor (SSRI) with other substrates of CYP 2D6 increases in serum concentrations of other medications, including beta-blockers such as labetalol (Normodyne), metoprolol, propranolol, and timolol and the type 1C antiarrhythmics such as encainide (Enkaid), flecainide (Tambacor), propafenone (Rythmol), and mexiletine (Mexitil) [19-34]. Fluoxetine is potent inhibitor of CYP 2D6 and co-administration of ypoglycem with insulin or oral ypoglycemic may produce hypoglycemia in patients with diabetes [19-23]. Duloxetine is a moderate inhibitor of 2D6 and Mirtazapine has no significant inhibitory or inductive capabilities [4].

Beta blockers and psychotropics

Propranolol, metoprolol, timolol, and alperolol are among the common beta blockers which are primarily metabolized by CYP2D6, Co-administration of beta blockers with antidepressants (substrates of CYP 2D6) such as selective serotonin reuptake Inhibitor (SSRI) increases in serum concentrations of beta blockers, including propranolol, timolol, labetalol and (Normodyne), metoprolol [19-23].

Common Medications, Nutrients and Substances Metabolized by Cytochrome CYP2D6, Inhibitors and Inducers of CYP2D6

CYP2D6 substrates are drugs metabolized by CYP2D6 enzyme subfamily. Drugs which are metabolized by CYP2D6 may inhibit or induce the action of the enzyme. Drugs that inhibit CYP2D6 will predictably increase the plasma concentrations of the medications or decrease in clearance of substrates. Drugs such as bupropion, fluoxetine, paroxetine, norethindrone, citalopram, escitalopram, sertraline, fluvoxamine, nefazodone, venlafaxine, clomipramine, cocaine, quinidine, and ranitidine are inhibitors of CYP2D6 enzyme [19-34].

Unlike CYP1A2, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 enzymes which together with CYP2D6 metabolize 90% of drugs CYP2D6 has no significant inducers [14,35].

Interactions that happen through CYP2D6 enzymes are either based on enzyme induction or inhibition. Drugs which induce CYP2D6 enzymes produce more of an enzyme which metabolized psychotropic medications. This reduces the amount of psychotropic medications, which may lead to loss of for psychotropic medication effectiveness. Drugs which inhibit CYP2D6 enzymes decrease the production of enzymes to metabolize psychotropic medications. This increases the amount of psychotropic medications in the body and could lead to an overdose or toxic effects. In addition, other drugs may function as inhibitors of CYP2D6 activity or inducers of CYP2D6 enzyme expression that will lead to decreased or increased CYP2D6 activity respectively. If such a drug is taken at the same time a second drug that is a CYP2D6 substrate, the first drug may affect the elimination rate of the second through what is known as a drug-drug interaction [10].

Understanding of drugs metabolized by CYP2D6 (substrates), inducers and inhibitors is vital for appropriate selection of significant drugs and the possible outcomes. In additions it is important to select drugs more effective for the patients especially in the case of concomitant use of medications (Table 2).

Substrate		Inhibitors		Inducers
Risperidone	Amitriptyline	Bupropion	Amiodarone	No significant inducers
Haloperidol	Codeine	Fluoxetine	Cimetidine	
Fluphenazine	Donepezil	Paroxetine	Iphenhydramine	
Sertindole	Metoprolol	Norethindrone	Chlorpheniramine	
Aripiprazol	Paroxetine	Citalopram	Demastine	
Zuclopentixol	Tramadol	Escitalopram	Perphenazine	
Clomipramine	Carvedilol	Sertraline	Hydroxyzine	
Desipramine	Timolol	Fluvoxamine	Tripelennamine	
Imipramine	Propranolol	Nefazodone	Chlorpromazi	
Thoredazine	Alprenolol	Venlafaxine	Clomipramine	
Methoxyamph	Amphetamine	Diphenhydramine	Cocaine	
Etamine	Atomoxetine	Quinidine	Quinidine	
Mexiletine	Bufuralol	Ritonavir	Ranitidine	
Nortriptyline	Chlorpheniramine	Terbinafine	-	
Minaprine	Chlorpromazine	-	-	
Ondansetron	Debrisoquine	-	-	
Perhexiline	Dexfenfluramin	-	-	
Ecaïnide	Dextromethorphan	-	-	
Flecainide	Metoclopramide	-	-	
Lidocaine	-	-	-	

Table 2: Summary cytochrome CYP2D6 substrates, inhibitors and inducers.

Conclusions

CYP2D6 is a member of the cytochrome P450 super family, is responsible for the metabolism of about 25% of the commonly prescribed drugs. Antidepressants, antipsychotics, mood stabilizers, antiarthemics, beta blockers antiemetics, opioid and Sedative/hypnotics are common drugs metabolized by CYP2D6. Drugs which are metabolized by CYP2D6 may inhibit or induce the action of the enzyme. Drugs that inhibit CYP2D6 will predictably increase the plasma concentrations of the medications or decrease in clearance of substrates.

Potential importance of genetic variability in drug response is generally acknowledged since many of the drugs metabolized by CYP2D6 are CNS active agents with narrow therapeutic indices, drug over treatment and accumulation can give rise to symptoms similar to those of the disease itself. Prescribers need to be aware of whether a drug they are prescribing is subject to pharmacogenetic variability and its importance and potential drug interactions. Concomitant use of this medication and inhibitors of these enzymes should be carried out with caution and adequate supervision. In addition, concomitant use of other drugs metabolized by same enzyme may predispose individual for side effects or reduce the effectiveness of the drugs. Prescribing advice should highlight the possibility of drug interactions when multiple drugs are prescribed concomitantly.

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