

# Involvement of Cytochromes P450 in Drug-Drug Interactions: An Overview

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## Summary

Drug interactions can cause iatrogenic disease. If concurrent medications are taken, the potential exists for a drug interaction to occur. Renewed interest in the topic of drug interactions has been generated by the fatal interactions involving non-sedating histamine H-1 antagonists and the recent introduction of two therapeutic agents, the selective serotonin reuptake inhibitors (SSRIs) and HIV protease inhibitors, for the treatment of depression and AIDS, respectively. These three therapeutic agents have been implicated in clinically significant drug interactions. The consequences of these interactions vary in clinical significance, extent, and effect. Some interactions are theoretical whereas others may lead to severe iatrogenic adverse experiences including lethal consequences. The purpose of this review is to alert the medical practitioner to potential drug interactions that may occur when these drugs are prescribed to patients. The pharmacological basis and clinical significance of these interactions are reviewed. The pharmacological mechanisms underlying these interactions are illustrative of those that may be involved for many other medications. Doctors should be aware of the potential pitfalls that may occur when certain groups of drugs are prescribed with concurrent medications.

**Key Words:** Drug metabolism, Cytochromes P450, Drug interactions

## Introduction

Drug interactions alter the expected pharmacological response to a drug when one or more other agents (such as food, chemicals, or drugs) are coadministered. This may either be of little significance or may cause a significant clinical event. Drug interactions are common but they may not get the attention they deserve.

Drugs may interact through different mechanisms. The more common ones can be classified on a pharmaceutic (i.e. product formulation), pharmacokinetic, or pharmacodynamic basis<sup>1</sup>. The most common mechanism for clinically important drug-drug interactions is pharmacokinetic interaction<sup>2,3,4</sup>. It occurs when the disposition (i.e. absorption, distribution,

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metabolism and excretion) of a drug is altered by another. Possible consequences of pharmacokinetic drug-drug interactions include the complexation of one drug to another, altering the amount of drug absorption (e.g. sucralfate and ciprofloxacin); displacement from protein binding sites, increasing the free, active concentration of one or both the drugs; and most importantly, the alteration of drug metabolism/excretion modifying the amount of drug available to bind to receptors. This process of modulating drug metabolism has proven to be one of the most important mechanisms accounting for the majority of serious consequences<sup>5,6</sup>. This is the primary mechanism basis which commonly prescribed drugs interact with other medications.

### The Basis for Metabolic-Based Drug Interactions

A number of organs are capable of metabolising drugs. In humans, drug metabolism occurs mainly in the liver, although the gut, kidneys, lungs, and brain are also capable of metabolising xenobiotics. Typically, drug metabolism occurs in two phases, Phase I (oxidation) and Phase II (glucuronidation) metabolism. Most drugs are metabolised by the liver, via the cytochrome P450 mixed-function oxidase system, a Phase I process<sup>7</sup>.

The largest quantities of cytochrome P450 (CYP) enzymes are located in the liver, although they are also found in the gut, kidneys, lungs, and brain. The CYP enzyme system is a supergene family with more than 14 primary enzymes and a number of isozymes of specific gene families<sup>7,8</sup>. The three primary families involved in human drug metabolism identified to date are CYP1, CYP2, and CYP3, specifically involving the CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 isozymes. Examples of substrates for these isozymes, their respective inducers, and inhibitors are illustrated in Table I. A single CYP can metabolise multiple substrates. This is responsible for many of the documented drug

interactions associated with CYP inhibition. The inhibition of drug metabolism by competition for the same enzyme may result in undesirable elevations in plasma drug concentrations. Inhibition of CYP enzymes is therefore of clinical importance for both therapeutic and toxicological reasons<sup>9,10</sup>. Drug interactions can also occur as a result of the induction of several human CYPs following prolonged drug treatment. Hence, recognition of the specific pathway by which a drug is metabolised by the CYP system allows the clinician to predict the possibility of an important drug-drug interaction.

This article emphasises drug interactions with some commonly used therapeutic agents relevant for ill patients. Particular attention is devoted to the effects of these drugs on the cytochrome P450 system, examining the potential for such effects to increase the likelihood of toxicity developing from both the agents and other concurrently administered drugs.

### Nonsedating Antihistamines

Terfenadine (Teldane™) was approved in United States in 1985. It is a nonsedating histamine H1-receptor antagonist that became the drug of choice for seasonal allergic rhinitis worldwide. Recognition that its elimination was predominantly determined by metabolism by CYP3A4<sup>4,11</sup> provided an explanation for several case reports in the early 1990s describing serious side effects, including that resulting from coadministration with ketoconazole and erythromycin<sup>12</sup>. Terfenadine is a prodrug. It undergoes extensive presystemic first-phase metabolism in the gut by CYP3A4 to active carboxylic metabolites, including fexofenadine. Terfenadine levels are not usually measurable in the plasma. Concurrent administration of drugs that inhibit terfenadine metabolism can however result in the accumulation of terfenadine. Terfenadine potentiates QT prolongation via inhibition of the delayed rectifier potassium channel in the cardiomyocyte (whereas the metabolites do not). This leads to an increased

risk of ventricular tachycardia and torsades de pointes<sup>12</sup>. Numerous prospective studies with many CYP3A4 inhibitors subsequently substantiated this<sup>13</sup>. Terfenadine has been thus removed from the market in the United States in 1997. Terfenadine, therefore, provides a classic example indicating the critical importance of drug metabolism and drug interaction in the development, regulation, and ultimate economic success of drugs.

CYP3A4 is also the predominant isozyme for the metabolism of astemizole<sup>14</sup>. Its metabolism is also significantly inhibited by ketoconazole, itraconazole, and erythromycin. Cases of prolonged QT-interval and syncope have been reported albeit rarely<sup>15</sup>. Consequently, the use of astemizole with CYP3A4 inhibitors is contraindicated. Interaction mechanisms involving cardiac electrophysiological events have also been reported for drugs from other therapeutic groups. Elevated plasma concentrations of cisapride, a serotonin agonist used in treatment of gastroesophageal reflux, following its administration with CYP3A4 inhibitors, have also been associated with QT prolongation and torsades de pointes, with at least 80 reported deaths<sup>16</sup>. For this reason, cisapride has recently been withdrawn from the US market and will only be prescribed on a limited-access basis.

### **Selective Serotonin Reuptake Inhibitors (SSRIs)**

The SSRIs have revolutionised psychopharmacology and now play an important role in treating psychiatric disorders. Since fluoxetine's (Prozac™, Eli Lilly Company, Indianapolis, USA) launch in 1988, similar new SSRIs have entered the market worldwide. The available SSRIs now include sertraline, paroxetine, fluvoxamine, and citalopram. These SSRIs have been extraordinarily useful because of their benign side effects, particularly their minimal quinidine-like properties, low or no

anticholinergic effects, and lack of effects on blood pressure. Although bradycardia has been attributed to fluoxetine, it is extremely rare in relation to its widespread use. Reports of adverse cardiac reactions with the SSRIs in the medically ill often describe patients with extensive concomitant medical illness and on multiple medications. This suggests that the adverse effects are probably due to drug interactions rather than direct effects of the SSRIs.

The SSRIs are metabolised by CYP enzymes. Each inhibits to some degree the isozyme responsible for its metabolism and, as such, may affect the disposition of other drugs metabolised by the same isozyme. It is however difficult to predict SSRI drug-drug interactions through the CYP system because of substrate specific characteristics in addition to specific SSRI characteristics. The SSRIs have variable impact on individual isozymes. For instance, they can inhibit CYP2D6 to some extent, even though they are not metabolised entirely by CYP2D6. Similarly, many substrate medications have alternate pathways that can become important if the principal isozyme is saturated.

Combination of an SSRI and a tricyclic antidepressant (TCA) is an example of an intentional drug-drug interaction used to increase treatment effect. On the other hand, unintentional pharmacokinetic interaction may lead to potentially dangerous untoward effects. Since a TCA is metabolized specifically by CYP2D6 that are inhibited by SSRIs, its serum level will increase when an SSRI is added. Increased serum levels of TCAs cause untoward symptoms that include sedation, constipation, tachycardia, hypotension, arrhythmia, and even death. Controlled measurements of SSRI-TCA interactions report a range of 40% to 300% increase in serum desipramine level when it was combined with an SSRI<sup>17,18,19</sup>. The potential impact of an SSRI on TCA metabolism depends on its pharmacokinetic profile and its potency as an inhibitor. Potency of SSRI inhibition of CYP2D6 has been measured extensively *in vitro*

and *in vivo* in adult populations. A rank order of SSRI inhibitory potency *in vivo* has been reported as follows: fluoxetine > sertraline > fluvoxamine<sup>20</sup>. Combination of *in vitro* and *in vivo* data produces a consistent rank order: paroxetine  $\geq$  fluoxetine  $\geq$  norfluoxetine > sertraline  $\geq$  fluvoxamine > citalopram<sup>21</sup>. Rank order of SSRI affinity at CYP2D6 shows fairly consistent trends among methods and researchers, i.e., paroxetine and fluoxetine prove more potent than sertraline, fluvoxamine, and citalopram<sup>22,23</sup>.

Other potentially dangerous pharmacokinetic interactions owing to metabolic inhibition include SSRIs used in combination with commonly prescribed agents such as theophylline and beta-blockers. There is a growing database which indicates that other isozymes are also inhibited by some SSRIs and are important in clinically relevant drug interactions. Fluvoxamine is unique among the SSRIs as a potent inhibitor of CYP1A2. It has been observed to increase serum concentrations of concomitantly administered CYP1A2 substrates, including theophylline<sup>24</sup>, haloperidol<sup>25</sup>, clozapine<sup>26</sup>, and imipramine<sup>27</sup>. Furthermore, the observation of increased serum concentrations of drugs metabolised by CYP2C isozymes, such as phenytoin, tolbutamide, and diazepam, during SSRI therapy suggests inhibition of these isozymes.

Table II compares important CYP isozymes, and potency of inhibition by each SSRI. The data in Table II were compiled from other reference tables<sup>28,29,30</sup> and are intended as an abbreviated reference to help predict specific SSRI drug-drug interactions. Clinically, it is prudent to suspect any SSRI as having a potential interaction at a given isozyme, particularly at higher dosages. In fact, norfluoxetine has greater *in vitro* affinity at CYP3A4 than fluoxetine. Codeine (a substrate of CYP2D6) represents an unusual aspect of CYP inhibition: codeine requires metabolism to an active metabolite that has analgesic properties. Inhibition of codeine metabolism by an SSRI may lead to insufficient analgesic effect.

In summary, the routine prescription of SSRIs in both children and adults, and utilisation in complicated psychiatric cases allow potentially complicated SSRI drug-drug interactions to occur. In clinical practice, it is reasonable to assume that SSRIs have the potential to increase levels of most medications used in combination. In general, most untoward effects owing to SSRI drug-drug interactions are mild symptoms related to increased serum concentration of medications used in combination with SSRIs. Therefore, it is important to know untoward effect profiles of SSRIs as well as other medications used in combination.

### HIV Protease Inhibitors

The development of inhibitors to the viral-encoded protease of HIV-1 has dramatically altered the clinical management of AIDS patients. Because AIDS is a set of complications arising from the immunodeficiency produced by HIV-1 infection, patients are almost invariably afflicted with opportunistic bacterial and fungal infections. This warrants treatment with antimicrobials (e.g. antibiotics, sulfonamides) and antifungals (e.g. ketoconazole, fluconazole), along with additional drugs for other AIDS-related conditions. This multidrug regimen increases the chance of drug interactions in AIDS patients<sup>31</sup>.

Numerous *in vitro* studies have shown that the first-generation protease inhibitors are excellent substrates for CYP3A4, and this has several implications. For instance, the relatively poor oral availability of HIV protease inhibitors (saquinavir < indinavir < nelfinavir < ritonavir) is in large part related to first-pass metabolism by CYP3A4 and possibly incomplete absorption associated with P-glycoprotein-mediated efflux transport in the small intestine<sup>32</sup>. Not unexpectedly, enzyme inducers such as rifampin markedly decreased the inhibitors' plasma levels (i.e. 80-90% reduction for saquinavir, indinavir, and nelfinavir, and 35% for ritonavir). Accordingly, therapeutic concentrations are not likely to be achieved, and

such coadministration is generally not recommended.

CYP inhibitors such as ketoconazole and clarithromycin, have been observed to modestly increase the plasma levels of ritonavir, indinavir, and nelfinavir, but generally not sufficient to warrant major dosage adjustments. On the other hand, the interaction of ketoconazole and saquinavir was found to be more pronounced, resulting in threefold increase in the protease inhibitor plasma levels. The inhibition by the protease inhibitors on other concurrently administered drugs has also been reported; for example, the plasma levels of rifabutin and its active metabolite increased two- to sixfold when either ritonavir, indinavir, or nelfinavir was coadministered. Thus, the concurrent use of HIV protease inhibitors with CYP3A substrates that have narrow therapeutic indices or those tend to cause serious side effects (e.g. terfenadine, astemizole, cisapride and midazolam) is not advisable and contraindicated.

Combination therapy involving more than one antiretroviral agents is now a standard treatment strategy in management of HIV infection. Preliminary studies, however, have already demonstrated that this will be complicated by pharmacokinetic interactions. Coadministration of usual doses of any two protease inhibitors typically increases the plasma levels of one of the agents by two- to eightfold, and in the case of ritonavir, this results in a twentyfold increase in saquinavir plasma levels<sup>33</sup>. Coadministration of these two protease inhibitors is currently being investigated as a strategy to improve the activity of saquinavir, which otherwise achieves marginal serum concentrations. The combination might prevent emergence of viral resistance and may prove beneficial to patients, as reduction of dosage requirement for saquinavir will minimize

the cost of long-term antiretroviral therapy.

## Conclusion

From the viewpoint of drug therapy, to avoid potential dangerous (or adverse) drug-drug interactions, it is desirable to use drugs that are not potent CYP inhibitors or inducers and are not readily inhibited by other drugs. In reality, drug interactions caused by mutual inhibition are almost inevitable, because CYP-mediated metabolism represents a major route of elimination of many drugs and because the same CYP isozyme can metabolise numerous drugs. Drug interactions involving CYP enzymes will undoubtedly continue to be of scientific interest and clinical importance.

It should, however, be emphasised that only a few drug interactions, but not all of them, are clinically significant. The clinical significance of a metabolic drug interaction will depend on the magnitude of the change in the concentration of active species (parent drug or metabolites) at the site of pharmacological action and the therapeutic index of the drug. In order to avoid untoward drug interactions, both the medical professional and the patient must be active participants. It is important for the medical practitioners to know the relevant pharmacological information for the drugs in their therapeutic armamentarium. The concept of prominent 'warning box' in drug manufacturer's package insert can be helpful in reducing the possibility of the risk of interaction. It is also helpful to have an updated "laundry" list of significant drug interactions in standard medical references such as Physician's Desk Reference and British National Formulary. Finally, a complete drug history before prescription of a drug is invaluable.

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**Table I**  
**Human xenobiotic-metabolising cytochromes P450**

| <b>CYP isozyme</b> | <b>Model substrates</b>  | <b>Model inhibitor(s)</b>  | <b>Model inducer</b>                   |
|--------------------|--|----------------------------|--|
| CYP1A2             | caffeine<br>phenacetin<br>heterocyclic<br>arylamines<br>theophylline                                     | furafylline<br>fluvoxamine | polycyclic<br>aromatic<br>hydrocarbons |
| CYP2C9             | tolbutamide<br>S-warfarin<br>phenytoin<br>diclofenac   | sulphaphenazole            | phenobarbital                          |
| CYP2C19            | S-mephenytoin<br>omeprazole<br>diazepam  | S-mephenytoin              |  |
| CYP2D6             | debrisoquine<br>sparteine<br>metoprolol<br>codeine<br>tricyclic<br>antidepressants                       | quinidine                  | non-inducible                          |
| CYP3A4             | nifedipine<br>midazolam<br>testosterone<br>cyclosporin A<br>terfenadine<br>erythromycin<br>carbamazepine | ketoconazole               | dexamethasone                          |



**Table II**  
**Inhibition of cytochromes P450 by selective serotonin reuptake inhibitors**

| <b>SSRI</b> | <b>CYP isozymes inhibited<sup>a</sup></b> | <b>Potential drug interactions<sup>b</sup></b>  |
|-------------|---|---|
| Fluoxetine  | CYP2D6 +++                                | secondary amine tricyclic antidepressants, haloperidol, type 1C antiarrhythmics               |
|             | CYP2C ++                                  | phenytoin, diazepam   |
|             | CYP3A4 +                                  | carbamazepine, alprazolam, terfenadine  |
| Sertraline  | CYP2D6 +                                  | secondary amine tricyclic antidepressants, antipsychotics, type 1C antiarrhythmics            |
|             | CYP2C +                                   | tolbutamide, diazepam   |
|             | CYP3A4 +                                  | carbamazepine   |
| Paroxetine  | CYP2D6 +++                                | secondary amine tricyclic antidepressants, antipsychotics, type 1C antiarrhythmics, trazodone |
| Fluvoxamine | CYP1A2 +++                                | theophylline, clozapine, haloperidol, amitriptyline, imipramine                               |
|             | CYP2C ++                                  | diazepam  |
|             | CYP3A4 ++                                 | carbamazepine, alprazolam, terfenadine  |

<sup>a</sup> degree of inhibition of SSRI on each isozyme is represented as follows: +++ substantial, ++ moderate, and + mild.

<sup>b</sup> data based on case reports and pharmacokinetic studies.

## MCQ.s on the Article Involvement of Cytochromes P450 in Drug-Drug Interactions: An Overview

1. Pharmacokinetic drug-drug interactions many include the following EXCEPT
  - A. Displacement of warfarin from binding sites on albumin by phenylbutazone
  - B. Formation of insoluble complex between iron and tetracycline retards absorption of the latter from the gut
  - C. Inhibition of cytochrome P450-mediated metabolism of terfenadine by ketoconazole results in cardiotoxicity of the antihistamine
  - D. Rifampicin reduces the effectiveness of warfarin as an anticoagulant by inducing metabolism of the latter
  - E. Some diuretics enhance action of digoxin by lowering plasma potassium concentration
2. Cytochromes P450
  - A. are located in the lipophilic environment of mitochondrial membranes
  - B. catalyses conjugation reactions
  - C. exhibit overlapping substrate specificities
  - D. only found in the liver
  - E. are not inducible by drugs
3. Reports of cardiac arrhythmias caused by unusually high blood level of terfenadine are best explained by
  - A. concomitant treatment with phenobarbital
  - B. use of this drug by smokers
  - C. a genetic predisposition to metabolise terfenadine slowly
  - D. treatment of the patient with ketoconazole
  - E. use of this drug by persons of Caucasian background
4. Fluvoxamine is unique among the SSRIs as a potent inhibitor of
  - A. CYP1A2
  - B. CYP2C9
  - C. CYP2C19
  - D. CYP2D6
  - E. CYP3A4
5. Which of the following statements regarding protease inhibitors is NOT true?
  - A. The protease inhibitors are subject to extensive first-pass metabolism by hepatic cytochrome P450 system
  - B. Many of the protease inhibitors are both substrates and inhibitors to CYP3A4
  - C. Saquinavir has been shown to increase the bioavailability of ritonavir substantially
  - D. It is prudent to avoid coadministration of protease inhibitors with other CYP3A4 substrates with narrow therapeutic indices
  - E. Protease inhibitors are also substrates to P-glycoprotein