Journal of Umm Al-Qura University for Medical Sciences 6 (1), (2020) 36-40

Journal of Umm Al-Qura University for Medical Sciences

journal homepage: https://uqu.edu.sa/en/mj

The Role of CYP 450 Isozymes in Drug-Drug Interaction

Fatmah A. Bakhdar[a].

[a] *Pharmacology Department, Pharmacy Collage, Umm Al-Qura University, Makkah, Saudi Arabia.*

ARTICLE INFO

Article History:
Submission date: 09/01/2019
Accepted date: 16/09/2019

Keywords:
CYP 450 Isozymes, Metabolism, Inhibitors, Inducer, Anticonvulsants, Antidepressant, Cardiovascular, Anti-infectives, Immunosuppressant.

ABSTRACT

The main focus of the pharmacokinetic process is hepatic metabolism, which is responsible for biotransformation and elimination of xenobiotics such as drugs. This step depends primarily on the CYP450 system, which plays a role in drug metabolism and changes their therapeutic responses. CYP450 enzyme system includes many notable points such as major families, their functions and also the factors that can alter their activity and cause significant interaction. According to previous studies, the most important factor affecting this enzyme system is the medications that can enhance or inhibit its activity.

The aim of this article is to discuss the detailed mechanism of the interaction between CYP450 enzyme and other drugs. This mechanism is very important when prescribing various medications to avoid the problem of drug-drug interaction**.**

We must remember that many drugs undergo metabolism through more than just isozyme interactions or may pass through dual metabolism pathways. Examples of such drugs are anticonvulsants, antidepressant, anti-infectives, immunosuppressant, and cardiovascular drugs.

1. Introduction

The adverse reaction of drug-drug interaction in the therapeutic system is of utmost importance. This can be a result of the change in metabolic enzymes.

Drugs pass through many processes to enhance their excretion from the body. One of these processes is metabolism which is done by several types of reaction such as reduction, oxidation, hydration, hydrolysis, isomerization, condensation, or conjugation [6]. While the rate of metabolism is affected by many factors such as chronic liver disease, genetic polymorphisms, or drug interactions [7], the metabolic processes result in the generation of inactive metabolites, or sometimes produce an active metabolite called a pro-drug, and of course, enzymes play a major role in this mechanism [8].

These enzymes are concentrated in the liver more than other tissues (extra-hepatic tissues) and are called the hepatic cytochrome P450 system. This system includes a group of enzymes that divide into families and subfamilies [9].

The enzyme system controls the main pharmacokinetic interactions of various medications. But some of the specific drugs can act as enzyme inhibitors or inducers when co-administrating with other drugs [10].

So the conception of this mechanism between enzyme and drug is very important when prescribing various medications. Finally, more research is needed to detect the alteration in individual enzymes to avoid or reduce the incidence of drug interactions and therefore decrease adverse effects [11].

2. Purpose

The main purpose of this research is to enhance our knowledge about the common role of CYP 450 isozymes in drug interactions.

3. Method

This review depends on research in reliable and popular medical databases which are PubMed, Saudi Digital Library, Google Scholar and Web of Science (ISI). The terms used to search the published research are isozymes, cytochrome P450 system, liver enzyme, drug metabolism, drug-drug interactions, enzyme inhibitors, and an enzyme inducer. The studies identified were published in 51 references which are distributed between the years 2008 to 2017.

3.1. Cytochrome P450 system

The P450 cytochrome system is controlled via the human genome 57 [12], which regulates more than twelve enzymes in three families using a coding system consisting of numbers and letters related to the system [13].

We can divide their functions into three portions. The first participates in the biosynthesis of signaling molecules and regulatory factors or sterols. The second is responsible for the metabolism and detoxify of the xenobiotics. But the role of the last is still unclear [14].

By focusing more, on the most important function of the system, which is biotransformation, that affects 70-80% of drugs. Where the drug undergoes the first-pass metabolism before entering to plasma this causes variation of the individual pharmacokinetics between people.

This function also helps the clearance of other products like tobacco, alcohol, and methamphetamine [15].

Generally, the CYP450 system involves several enzymes regulated in CYP1, 2, and 3 groups, each of which plays a role in metabolism for roughly two-thirds of discovered drugs. Usually metabolism results in the release of reactive oxygen species called prodrug. Toxic metabolites are also sometimes released [16]. Among them, CYP1A2, 3A4, 2C8, 2C9 and 2E1 which are present in high concentrations in the liver whereas CYP2A6, 3A5, 2B6, 2C19, and 2D6 exist in low concentration, but CYP1A1, 1B1, 2J2,2S1 and 2W1 are extrahepatic enzymes that appear in certain tissues like hypoxic or tumor tissues [17]. Factors that can alter the activity of enzymes must be taken into consideration e.g. gene polymorphisms for CYP450 which effect the action of CYPs 2A6, 3A5, 2B6,2C9, 2C19 and 2D6 [18]. The other notable factors are received xenobiotics like specific medication or food, disease condition, age, sex, hormones and cytokines regulation [16].

More precisely, these factors may enhance the activity of enzymes (called hyper or extensive) and change their reactions resulting in

* **Corresponding Author**
Pharmacology Department, Pharmacy College, Umm Al-Qura University, Makkah, Saudi Arabia.
E-mail address: abaqmajd@gmail.com
1685-4732 / 1685-4740

reduced bioavailability and plasma concentration and so reduced efficacy of the drugs.

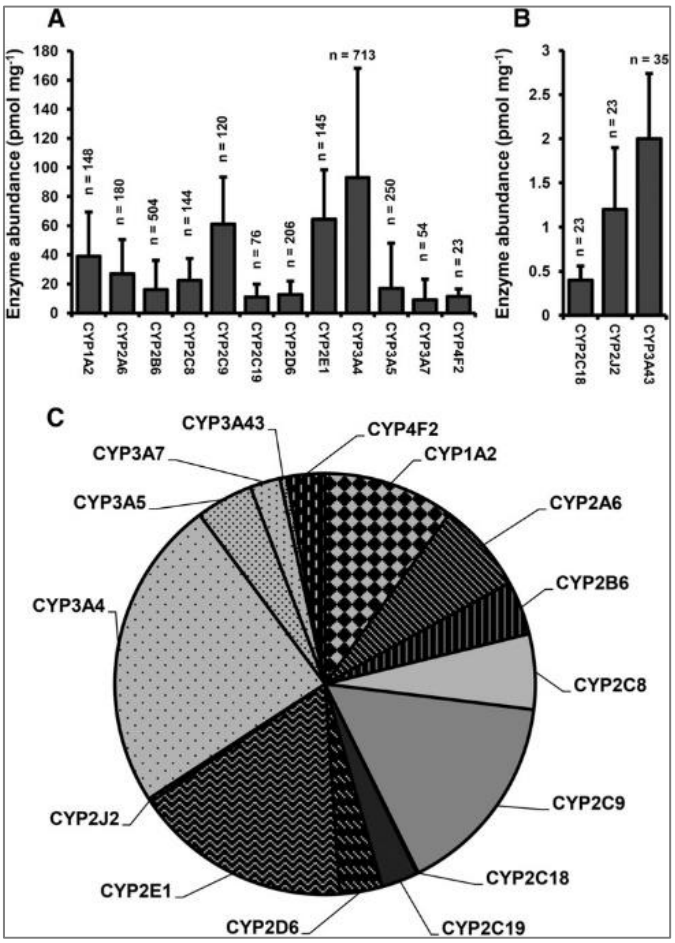

Fig 1: Types of cytochrome P450 enzymes [5]

But the positive thing is decreased toxicity and reduced access to the brain. On the other hand, they may reduce the activity of individual enzymes and cause the opposite action to the above [19].

Table 1: Specific cytochrome P450 enzymes and drug substrates with its inhibitors and inducer [3]

CYP450 Enzyme	Common drug substrates	Inhibitors	Inducers
CYP1A2	Clozapine, Estrogen, Clomipramine, Fluvoxamine, Haloperidol, Theophylline, Tacrine	Amiodarone, cimetidine, fluoroquinolones, ticlopidine	Olycyclic aromatic hydrocarbon, Omeprazole, Ritonavir, Phenobarbital
CYP3A	Diltiazem, Nifedipine, Felodipine, Verapamil, Tacrolimus, Sildenafil, Cyclosporin, Alprazolam, Triazolam, Midazolam, Ritonavir, Atorvastatin, Clarithromycin, Losartan, Erythromycin, Indinavir.	Troleandomycin, Itraconazole, Verapamil, Ketoconazole, Mifepristone, Clarithromycin, Nefazodone, Erythromycin, Diltiazem, Delavirdine, Indinavir, Ritonavir, Saquinavir, Grapefruit juice.	Rifapentine, Rifampin, Rifabutin, St John's Wort, Carbamazepine, Phenytoin, Phenobarbital, Nevirapine, Efavirenz, Topiramate.
CYP2C9	Phenytoin, Tolbutamide, Warfarin, Glipizide.	Amiodarone, Miconazole, Fluconazole, Phenylbutazone, Sulphinpyrazone.	Phenobarbital, Rifampin, Carbamazepine, St John's Wort.
CYP2E1	Paracetamol, Ethanol, Benzene, Theophylline, Isoflurane.	Diethyl-dithiocarbamate, Disulfiram.	Isoniazid, Ethanol.
CYP2D6	Alprenolol, Carvedilol, Bufuralol, Metoprolol, Timolol, Propranolol, Amitriptyline, Desipramine, Clomipramine, Imipramine, Flecainide, Nortriptyline, Mexiletine, Fluoxetine, Propafenone, Haloperidol, Perphenazine, Paroxetine, Codeine, Venlafaxine, Dextromethorphan.	Clomipramine, Fluoxetine, Quinidine, Paroxetine, Haloperidol.	Not inducible.

3.2. Main Mechanism of Cytochrome P450 system

Cytochromes P450, which was discovered in 1958, is a family of cysteine thiolate-ligated heme that containing monooxygenase enzyme [20]. It catalyzes the movement of the oxygen atom from the oxygen molecule creating broad species of substrates as part of the oxidation reaction. It also reduces the second O_2 by 2 electrons to create water molecules that causes an interaction of NADPH [21]. The reaction can be explained in this simple equation:

(1) RH + (1) NAD(P)H + (1) O_2 + H^+ → (1) ROH + (1) $NAD(P)^+$ + (1) H_2O (2)

Now, we focus on the mechanism of these enzymes in metabolism. First, they can add O_2 to N-H or C-H bond to produce hydroxyl derivative and the usual terminal product is alcohol (22), but the hydroxylation in C-H bond that is attached to the heteroatom produces fragments which are carbonyl groups with others like hydroxyl, thiol or amine groups, and this is the major method of P450 in catalyzing prodrug generation [23].

Secondly, the enzymes can accelerate the epoxidation of olefinic bonds and also aromatic π-bonds, and finally, they can bond O_2 with sulfur or nitrogen atoms (in electron pair) to produce S-oxide or N-oxide molecules [24].

In summary, the most oxidation reactions are hydroxylation, heteroatom oxidation, epoxidation, and heteroatom dealkylation [25].

4. Significant drug interactions affected by CYP system

The widely known major therapeutic metabolic enzyme is CYP3A4. In addition to its known actions, it can metabolism various narcotics like cocaine and methamphetamine, whilst the metabolic enzymes for nicotine, alcohol, and polyaromatic-hydrocarbon are CYP2A6, CYP2E1, and CYP1A1/1B1 [26].

We must remember that several drugs undergo metabolizism through more than just one isozyme, or in other words they pass through dual metabolism pathways [16].

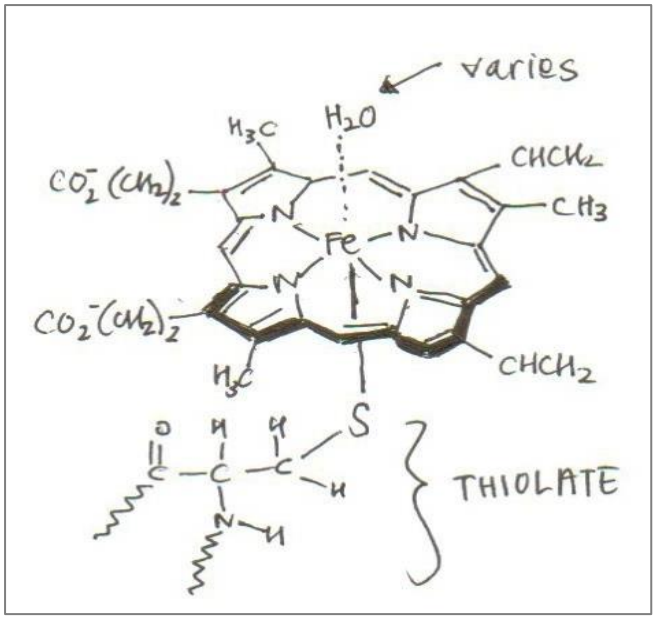

Fig 2: Chemical structure of cytochrome P450 [2].

4.1. Anticonvulsants Drugs

CYP3A4 is induced by phenytoin, oxcarbazepine, and carbamazepine that stimulates metabolism and causes a decrease in the concentration of oral contraceptives that can lead to unplanned pregnancies [27].

So, many clinical effects of critical drugs like cyclosporin or warfarin, that have low therapeutic index, are changed and desired effects are reduced when taken at the same time with these drugs [28].

But if inhibitor drugs like verapamil are taken, they can decrease the rate of metabolism which can lead to the raising of carbamazepine concentration and the result is an increase in toxicity [29].

4.2. Antidepressant Drug

Most psychiatrists have a perception about certain parts of antidepressants' structure which can generate critical drug interactions due to inhibition of a CYP2D6 enzyme [30]. These can be enumerated as follows: escitalopram, citalopram, paroxetine, fluoxetine, fluvoxamine, mirtazapine, venlafaxine, desvenlafaxine, and vilazodone [31]. The FDA advises that if possible, genetic testing is required before starting treatment with certain SSRIs like paroxetine, fluoxetine, and fluvoxamine, to determine the individual activity of CYP2D6 [32].

The effect of fluvoxamine, which is a potent inhibitor, appeared when received with codeine, which inhibits it, to convert it to morphine by inhibiting CYP2D6 enzyme resulting in the loss of painkiller effect [33].

On the other hand, the different effect of inhibition of CYP2D6 enzyme is shown in plasma concentration, in which clozapine and carvedilol levels are increased by 30–42%, whilst galantamine, metoprolol, risperidone, and donepezil levels are increased by 2 to 5 fold [34]. The effects of warfarin can be increased when combined with antidepressants, due to an inhibition of metabolism that leads to an increased risk of bleeding [35]. Harvard medical school reported, that the combination of antidepressants and tamoxifen can cause interference with the benefit of breast cancer treatment due to inhibition conversion of tamoxifen to endoxifen as active form [36].

Antiepileptic Drugs	Major Hepatic Enzymes
Carbamazepine	CYP3A4; CYP1A2; CYP2C8
Ethosuximide	CYP3A4
Felbamate	CYP3A4; CYP2E1; other
Gabapentin	None
Lacosamide	CYP2C19
Lamotrigine	GT
Levetiracetam	None (undergoes non-hepatic hydrolysis)
Oxcarbazepine (MHD is active oxcarbazepine metabolite)	Cytosolic system
Phenobarbital	CYP2C9; other
Phenytoin	CYP2C9; CYP2C19
Pregabalin	None
Rufinamide	Hydrolysis
Tiagabine	CYP3A4
Topiramate	Not known
Valproate	GT; β-oxidation
Vigabatrin	None
Zonisamide	CYP3A4

Fig 3: Major cytochrome P450 effect antiepileptic drugs [1].

4.3. Anti-infectives Drugs

In general, ketoconazole, miconazole and itraconazole are famous antifungals which inhibit all CYP450 enzymes and cause numerous critical interactions [37]. They can increase the concentrations of other medications specially drugs with low therapeutic index like cyclosporin, digoxin, erythromycin and also warfarin for which they increase INR level and cause an increased risk of bleeding [38].

On the contrary, rifampicin is an example of an enzyme inducer that decreases the concentration of other drugs by stimulating metabolism and enhancing clearance. So, it must be noted when prescribed with other drugs like digoxin, aprepitant, ranolazine, tacrolimus, sulfasalazine, and theophylline [39].

4.4. Cardiovascular Drugs

From the many antihypertensive drugs, the calcium channel blocker (CCB) is a familiar prescription for several conditions other than hypertension like angina, heart failure, coronary artery and arrhythmia disease.[40]

Felodipine is one of the CCB and its concentration is affected via CYP3A4 enzyme inhibitors such as ritonavir, itraconazole, and erythromycin that lead to increased concentration and may cause rapid hypotension in some patients [41], while in epileptic patients receiving carbamazepine, which is a CYP3A4 enzyme inducer, it is necessary to take felodipine with high dose to achieve its effect [42].

Other examples of CCB are verapamil and diltiazem, which are considered as moderate CYP3A4 enzyme inhibitors, and they can increase concentrations and effects of other drugs especially low therapeutic index drugs, which, when taken at the same time like warfarin increases the risk of hemorrhage [43].

Pimozide or cisapride can produce QT prolongation and ventricular arrhythmias when taken with diltiazem or verapamil. This occurs due to inhibition of metabolism and accumulated drugs that lead to excessive side effects [44]. Also, fentanyl is the other drug that has significant drug interaction with verapamil, which leads to an increase in blood levels of the drug and therefore a rise in its effects [45].

The other group of therapy is statin drugs like atorvastatin, simvastatin, and lovastatin that are used to lower hyperlipidemia, but they must be taken with caution if prescribed with CYP3A4 enzyme inhibitors such as erythromycin, ritonavir, nefazodone and grapefruit juice to avoid incidence of rhabdomyolysis which is a serious side effect due to an increase in the concentration of statins [46].

One of the famous drugs with critical drug interactions is warfarin because it has a complex pathway in CYP450 metabolism, so it needs frequent monitoring for INR to confirm the steady state of plasma concentration [47]. Clinical studies investigating the combination of warfarin with amiodarone, which is the antiarrhythmic drug, showed a significant drug interaction. Warfarin blood levels were increased by between 6 and 65% as a result of the resultant decrease metabolism of warfarin via amiodarone, leading to increased risk of bleeding [48]. However, other cases of warfarin drug interaction occur when co-administred with primidone. Primidone has a broad spectrum as an enzyme inducer and can affect the activity of many subfamilies such as CYP3A4, CYP2C9, CYP1A2, and CYP2C19. So, the result of the interaction is to decrease the INR level and therefore the anticoagulant activity of warfarin through increasing its clearance [28].

4.5. Immunosuppressants Drugs

According to clinical studies, the combination of immunosuppressant with some enzyme inhibitors can benefit the patient and help to give him a low dose of immunosuppressant drugs. For example, the physician can add ketoconazole to the therapeutic plan contain cyclosporin because it has the highly active CYP3A4 enzyme inhibitor and can therefore decrease the dose of cyclosporin [49]. Furthermore, if the plan combines cyclosporin and St John's wort, which is a CYP3A4 enzyme inducer, the result generates a sequence of organ loss by rejection [50]. The clinical observation reported about the co-administration of CYP3A4 enzyme inhibitors like diltiazem with tacrolimus, can increase the concentration and raise toxicity risk of tacrolimus [51]. Conversely, if the tacrolimus combines with CYP3A4 enzyme inducers like carbamazepine, the concentration of tacrolimus will decrease and the toxicity risk will reduce [52].

4.6. Grapefruit juice:

It is important to note, and usually the physician will warn patients to avoid drinking grapefruit juice before medication due to its characteristic inhibitory action on CYP3A that causes a rise in the concentration, bioavailability and also side effects of many drugs [53]. According to research at the University of California, scientists compared the potency between grapefruit and cannabinoid (CBD) and it showed that CBD is as highly a potent inhibitor as grapefruit [54].

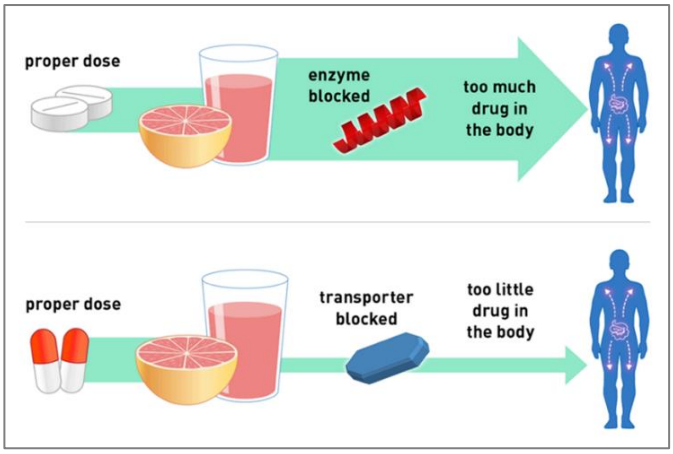

Fig 4: Effect of grapefruit in metabolism of drugs [4].

5. Conclusions

Metabolic enzymes are the main player in drug-drug interactions that cause individual variation of drug response. The major hepatic enzyme family is the CYP system, which has more than twelve enzymes

regulated in three groups and they are responsible for biotransformation and elimination of 70-80% of marketed drugs.

Each enzyme has a specific inducer and inhibitor drug but the critical enzyme is CYP3A4 which is then followed by CYP2D6, CYP1A2, CYP2C9, and CYP2E1.

The safest method to define metabolic interactions of drugs is by understanding the rules controlling interactions. Drugs which inhibit CYP450 can decrease metabolism rate and therefore increase the activity of other drugs and occasionally raise toxicity when taken at same time.

But, the enzyme inducer drugs that are stimulators of metabolism can cause a decrease in concentration and activity of other drugs.

So, special attention should be given to drugs that have a low therapeutic index or have severe adverse effects like antibiotic, immunosuppressant, anticonvulsants or cardiovascular drugs.

However, researchers are investigating the positive applications of some of the drug-drug interactions in the therapeutic field, to take advantages of actions like a reduction in drug dose or minimizing the occurrence of serious side effects for prescribed drugs.

6. Reference

[1] Rogers SJ CJ. DiPiro's Pharmacotherapy: 8th Edition, McGraw-Hill; 2011.

[2] Chemistry L. Cytochrome P450 University of California 2015 [Available from: https://chem.libretexts.org/LibreTexts/University_of_California_Davis/UCD_Chem_124A%3A_Berben/Cytochrome_P450/Cytochrome_P450_3.

[3] Rodes J, Benhamou J-P, Blei A, Reichen J, Rizzetto M. The textbook of hepatology: from basic science to clinical practice. 3ed ed: Wiley-Blackwell; 2008.

[4] Phillips B. How Grapefruit Juice Affects Drugs HEALTH CARE PROFESSIONALS COMMUNITY: FDA's Consumer Updates page; 2017 [Available from: http://www.shieldhealthcare.com/community/health_care_professionals/2017/07/20/how-grapefruit-juice-affects-drugs/.

[5] Brahim Achour JB, Amin Rostami-Hodjegan. Expression of Hepatic Drug-Metabolizing Cytochrome P450 Enzymes and Their Intercorrelations: A Meta-Analysis. Drug Metabolism and Disposition. 2014;42(8):1349-56.

[6] Robertson D, Maibach H, Katzung B, Trevor A. Basic and Clinical Pharmacology. 13th ed. United States of America: McGraw-Hill Education; 2015.

[7] Le J. Drug Metabolism. University of California San Diego: Skaggs School of Pharmacy and Pharmaceutical Sciences; 2016.

[8] Rang HP, Ritter JM, Flower RJ, Henderson G. Rang & Dale's Pharmacology. 8th ed. British: Elsevier Health Sciences; 2016.

[9] NursingLink. Clinically Significant Drug Interaction with the Cytochrome P450 Enzyme System 2017 [Available from: http://nursinglink.monster.com/training/articles/320-clinically-significant-drug-interaction-with-the-cytochrome-p450-enzyme-system.

[10] Miksys S, Tyndale RF. Cytochrome P450-mediated drug metabolism in the brain. Journal of Psychiatry & Neuroscience. 2013;38(3):152-63

[11] 11. Kebamo S, Tesema S, Geleta B. The role of biotransformation in drug discovery and development. Journal of Drug Metabolism & Toxicology 2015;6(196):2.

[12] Pikuleva IA, Waterman MR. Cytochromes P450: roles in diseases. Journal of Biological Chemistry. 2013;288(24):17091-8.

[13] Alan L. Drug Interactions: A Matter for Enzymes: Canadian Society of Intestinal Research 2017 [Available from: http://www.badgut.org/information-centre/a-z-digestive-topics/drug-interactions-a-matter-for-enzymes/.

[14] Communications LHNCfB. Genetics home reference: Cytochrome p450. In: Services DoHH, editor. National Institutes of Health: National Library of Medicine; 2017.

[15] Drugs and the liver: Metabolism and mechanisms of injury [Internet]. UpToDate, Wolters Kluwer Health. 2016.

[16] Coleman MD. Human drug metabolism: an introduction. 2nd ed: John Wiley & Sons; 2010.

[17] Nebert DW, Wikvall K, Miller WL. Human cytochromes P450 in health and disease. Philosophical Transactions of the Royal Society B. 2013;368(1612):2012.0431.

[18] Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Journal of Pharmacology & therapeutics 2013;138(1):103-41.

[19] Hukkanen J. Induction of cytochrome P450 enzymes: a view on human in vivo findings. Expert review of clinical pharmacology. 2012;5(5):569-85.

[20] Yosca TH, Ledray AP, Ngo J, Green MT. A new look at the role of thiolate ligation in cytochrome P450. Journal of Biological Inorganic Chemistry. 2017;22(2-3):209-20.

[21] Shakunthala N. New cytochrome P450 mechanisms: implications for understanding molecular basis for drug toxicity at the level of the cytochrome. Expert opinion on drug metabolism & toxicology. 2010;6(1):1-15.

[22] Perin ML. Biotransformation of Drugs: Definition, Types & Process 2017 [Available from: http://study.com/academy/lesson/biotransformation-of-drugs-definition-types-process.html#transcriptHeader.

[23] Ortiz de Montellano PR. Cytochrome P450-activated prodrugs. Journal of Future medicinal chemistry. 2013;5(2):213-28.

[24] Hrycay EG, Bandiera SM. The monooxygenase, peroxidase, and peroxygenase properties of cytochrome P450. Archives of biochemistry and biophysics Journal. 2012;522(2):71-89.

[25] Guengerich FP, Munro AW. Unusual cytochrome P450 enzymes and reactions. Journal of Biological Chemistry. 2013;288(24):17065-73.

[26] Kumar S. Plasma Exosomes and Drug Metabolic Cytochrome P450 Enzymes. Journal of Drug Metabolism and Toxicology. 2015;5(1):e124.

[27] Johannessen S, Johannessen Landmark C. Antiepileptic drug interactions-principles and clinical implications. Current neuropharmacology Journal. 2010;8(3):254-67.

[28] Marie AY, Bostwick JR, Hallman IS. Warfarin drug interactions: strategies to minimize adverse drug events. The Journal for Nurse Practitioners. 2011;7(6):506-12.

[29] Authority NZMaMDS. Drug Metabolism - The Importance of Cytochrome P450 3A4. New Zealand Ministry of Health; 2014. p. 4–6.

[30] Mago R. Reducing CYP45O Drug Interactions Caused by Antidepressants. Current Psychiatry Journal. 2012;11(9):55.

[31] Caraci F, Crupi R, Drago F, Spina E. Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. Journal of Current drug metabolism. 2011;12(6):570-7.

[32] Selective Serotonin Reuptake Inhibitors and CYP2D6 [Internet]. Medscape. 2016.

[33] Horn J, Hansten PD. Codeine drug interactions. Pharmacy Times Journal. 2014;80(11).

[34] Bleakley S. Antidepressant drug interactions: evidence and clinical significance. Progress in Neurology and Psychiatry. 2016;20(3):21-7.

[35] Allen SN, Ferrara J, John S, Shannon J. Treatment of depression in patients on anticoagulation therapy: Antidepressant-warfarin drug interactions. US Pharmacist Journal. 2013;38(11):23-6.

[36] Antidepressants and tamoxifen [Internet]. Harvard Medical School of Harvard University. 2010. Available from: http://www.health.harvard.edu/newsletter_article/antidepressants-and-tamoxifen.

[37] Candidiasis Medication: Azole antifungals [Internet]. Medscape. 2016. Available from: http://emedicine.medscape.com/article/213853-medication.

[38] Sanford g. Updated Treatment Guidelines: Concomitant treatment of an anti-infective agent with warfarin: Sanford Guide; 2016 [Available from: https://www.sanfordguide.com/january-id-update/.

[39] Castro JB, Sinha S. Rifampin review 2015 [Available from: http://www.everydayhealth.com/drugs/rifampin.

[40] Rodriguez D, Jasmer R. Calcium Channel Blockers Review 2016 [Available from: http://www.everydayhealth.com/calcium-channel-blocker/guide/.

[41] Horn JR, Hansten PD. DRUG INTERACTIONS-CCBS and CYP3A4 Inhibitors: Watch Out for Enhanced Cardiovascular Response. Pharmacy Times Journal. 2011;77(6):48.

[42] Prescriber DR. Felodipine - Drug Summary 2017 [Available from: http://www.pdr.net/drug-summary/Felodipine-felodipine-1398#topPage.
[43] Common Medications Classified as Weak, Moderate and Strong Inhibitors of CYP3A4 [Internet]. Evidence Based Medicine Consult. 2015.
[44] Wiśniowska B, Tylutki Z, Wyszogrodzka G, Polak S. Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect-comprehensive overview of clinical trials. BMC Pharmacology and Toxicology. 2016;17(1):12.
[45] Trescot AM. Opioid Pharmacology and Pharmacokinetics. Controlled Substance Management in Chronic Pain: Springer; 2016. p. 45-62.
[46] Kellick KA, Bottorff M, Toth PP. A clinician's guide to statin drug-drug interactions. Journal of clinical lipidology. 2014;8(3):S30-S46.
[47] Teklay G, Shiferaw N, Legesse B, Bekele ML. Drug-drug interactions and risk of bleeding among inpatients on warfarin therapy: a prospective observational study. Thrombosis journal. 2014;12(1):20.
[48] McDonald M, Au N, Wittkowsky A, Rettie AE. Warfarin–Amiodarone Drug–Drug Interactions: Determination of [I] u/KI, u for Amiodarone and Its Plasma Metabolites. Clinical Pharmacology & Therapeutics. 2012;91(4):709-17.
[49] Berdaguer S, Bautista J, Brunet M, Cisneros JM. Antimicrobial and immunosuppressive drug interactions in solid organ transplant recipients. Enfermedades Infecciosas y Microbiología Clínica. 2012;30(2):86-92.
[50] Kotsirilos V, Vitetta L, Sali A. A guide to evidence-based integrative and complementary medicine: Elsevier Australia; 2011.
[51] Li J, Wang X, Chen S, Liu L, Fu Q, Chen X, et al. Effects of diltiazem on pharmacokinetics of tacrolimus in relation to CYP3A5 genotype status in renal recipients: from retrospective to prospective. The pharmacogenomics journal. 2011;11(4):300-6.
[52] Patsalos P. Antiepileptic drug interactions: a clinical guide. 3ed ed: Springer; 2016.
[53] Hanley MJ, Cancalon P, Widmer WW, Greenblatt DJ. The effect of grapefruit juice on drug disposition. Expert opinion on drug metabolism & toxicology. 2011;7(3):267-86.
[54] Lee AD. CBD-Drug Interactions: Role of Cytochrome P450: Project CBD; 2015 [Available from: https://www.projectcbd.org/article/cbd-drug-interactions-role-cytochrome-p450.