WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 14, 439-448. Review Article ISSN 2277– 7105

THE ROLE OF CYTOCHROME P450 IN DRUGMETABOLISM

Ayodhya B. Khedkar*, Shrikant P. Gavhale., Shubhangi D. Narsale

India.

Article Received on
24 June 2023,

Revised on 15 July 2023,
Accepted on 05 August 2023

DOI: 10.20959/wjpr202314-29329

***Corresponding Author**
Ayodhya B. Khedkar
India.

ABSTRACT

Cytochrome P450 is a family of isozymes responsible for the biotransformation of several drugs. Drug metabolism via the cytochrome P450 system has emerged as an important determinant in the occurrence of several drug interactions that can result in drug toxicities, reduced pharmacological effect, and adverse drug reactions. Recognizing whether the drugs involved act as enzyme substrates, inducers, or inhibitors can prevent clinically significant interactions from occurring. Avoiding coadministration or anticipating potential problems and adjusting a patient's drug regimen early in the course of therapy can provide optimal response with minimal adverse effects.

KEYWORDS: Hemeprotein, substrate, inhibitors, xenobiotics, allosteric site, Prosthetic site, ligand, isoforms.

KEYPOINTS: CYP450 enzymes are responsible for the metabolism of 90% of the drugs seen in clinical practice with CYP3A4 and CYP2D6 being the most significant enzyme.

INTRODUCTION

1. Cytochrome P450 (CYP) is a hemeprotein that plays a key role in the metabolism of drugs and other xenobiotics.
2. Drug metabolism occurs in many sites in the body, including the liver, intestinal wall, lungs, kidneys, and plasma.
3. As the primary site of drug metabolism, the liver functions to detoxify and facilitate excretion of xenobiotics (foreign drugs or chemicals) by enzymatically converting lipid-soluble compounds to more water-soluble compounds.
4. Drug metabolism is achieved through phase I reactions, phase II reactions,or both.
5. The most common phase I reaction is oxidation, which is catalyzed by theCYP system.

Classification

Cytochrome P450 pathways are classified by similar gene sequences; they are assigned a family number (e.g., CYP1, CYP2) and a subfamily letter (e.g., CYP1A, CYP2D) and are then differentiated by a number for the isoform or individual enzyme (e.g., CYP1A1, CYP2D6).[1]

Enzyme inhibition and its type

I) Enzymes are proteins that help speed up metabolism, or the chemical reactions in our bodies.[2]

II) Enzymes are essential for digestion, liver function and much more our bodies naturally produce enzymes. But enzymes are also in manufacturedproducts and food.[2]

III) The enzyme specificity is determined by the active site, a particular domain of the peptide molecule.[2]

Two main type of inhibition1.Reversible

2. Irreversible

The enzyme inhibitors are molecules e. It has a hole (active site) in which a substance (substrate) can be transformed into another compounds.

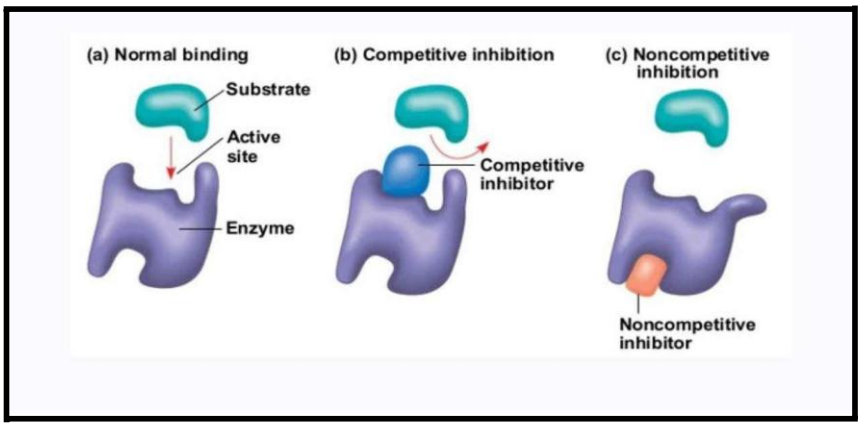

Fig. 1: The Role of Cytochrome P450 in Drug Metabolism.

1. Reversible inhibition

i) It occurs as a result of competition at the active site of the enzyme

ii) It involves only the first step of the P450 catalytic cycle.[3]

iii) Binding to the enzyme takes place usually with weak bonds, which are bothformed and broken down easily.[3]

iv) Reversible inhibitors act rapidly, but do not permanently destroy theenzyme.[3]

v) It's act by two mode- a)competitive inhibition b)Noncompetitive inhibition,

c) Mixed inhibition

a) Competitive inhibition

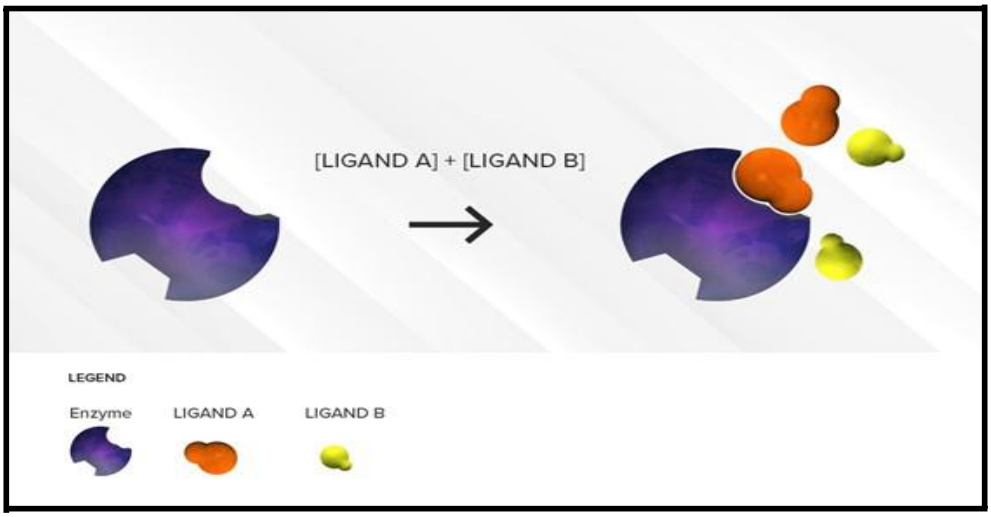

Fig. 2: The competitive inhibition.

The competition between the substrate and inhibitor to bind to the same position on the active site of the enzyme takes place. Reversible competitive inhibition where ligand A (orange) is a substrate with strong affinity and ligandB (yellow) is a substrate with weaker affinity for a specific enzyme (purple)[4] Eg. Metoprolol Propafenone

b) Noncompetitive inhibition

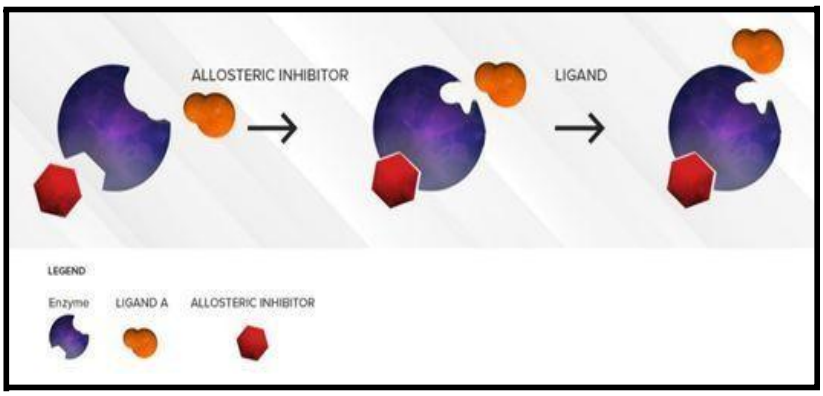

Fig. 3: The Noncompetitive inhibition.

The active binding site of the substrate and inhibitor is different from each other. An inhibitor (red) binds to an allosteric site on the enzyme and causes conformational changes that prevent a substrate (orange) from binding to theactive site.[5] [6]

Eg. Fluvoxamine terbinafine

c) Mixed inhibition

In the case of mixed inhibition, both competitive and non-competitive inhibition occur. Mixed inhibitors can simultaneously bind to both the heme iron atom (at the active site) and lipophilic regions of the protein (allosteric site). Mixed inhibitors are usually more potent inhibitors than competitive or non-competitive inhibitors. [7]

Eg. KetoconazoleFluconazole

2) Irreversible inhibition

Fig. 4: The Irreversible Inhibition.

i) It's also known as mechanism based inhibition[8,9]

ii) It generally derives from the activation of a substrate drug by a CYP450isoform into a reactive metabolite.[8,9]

iii) It binds to the enzyme heme prosthetic site (part of the active site), resulting in irreversible long-lasting loss of enzyme activity.[8,9]

iv) The mechanism-based inhibitor (orange) binds to the active site as asubstrate.[8,9]

v) During the normal process of metabolism, it forms either stable intermediate–enzyme complexes or reactive electrophilic species that can destroy the enzyme and new enzyme synthesis is required to restore the enzymatic activity[8,9]

vi) In the case of irreversible inhibition, the metabolites form very stable complexes with the heme prosthetic site so that the enzyme is sequestered ina functionally inactive state.[8,9]

vii) In the case of irreversible inhibition, the metabolites covalently bind to the heme prosthetic site or the protein part of the CYP450, leading to irreversible inactivation[8,9]

viii) Hence, mechanism-based inhibition is active site mediated, and theallosteric site is not involved.[8,9]

ix) In contrast to reversible inhibition mechanisms, mechanism-based inhibition is time dependent and NADPH dependent.[8,9]

x) Mechanism-based inhibitors can be classified into two categories:

a) metabolic intermediate complex formation inhibitors b)proteins and heme alkylation inhibitors.

a) Metabolic–Intermediate Complex Formation (or Alternate Substrate Inhibition)- a condition occurs when a stable intermediate metabolite formed during the normal metabolic cycle forms covalent bonds at the active site.[10,11,12]

1) This stable intermediate enzyme complex is not easily broken by increasing substrate concentration.[10]
2) Since the enzyme structure remains otherwise unchanged, theoretically this reaction is reversible with time.[10,11,12]

Eg. paroxetin clarithromycin

b) Protein and/or Heme Alkylation (or Suicide Inhibition)

This situation takes place when a latent highly reactive (generallyelectrophilic) intermediate is formed in the catalysis process.[13]

1) The reactive intermediate forms covalent bonds (strong irreversible bonds) with the enzyme in a step that is not part of the normal metabolic pathway.[13]
2) This process can change the conformational structure of the enzyme.[13]
3) It can even destroy the enzyme ,in some cases making it functionallyunviable.[13]

Eg. EsomeprazoleDrug interactions -

Table 1: Significant Cytochrome P450 Enzymes and Their Inhibitors, Inducers, and Substrates.

Enzyme	Potent inhibitors	Potent inducers	Substrates
CYP1A2	Amiodarone (Cordarone), cimetidine (Tagamet), ciprofloxacin(Cipro), fluvoxamine (Luvox)	Carbamazepine (Tegretol), phenobarbital, rifampin (Rifadin), tobacco	Caffeine, clozapine (Clozaril), theophylline
CYP2C9	Amiodarone,fluconazole (Diflucan), fluoxetine (Prozac), metronidazole (Flagyl), ritonavir(Norvir), trimethoprim/sulf amethoxazole (Bactrim,	Carbamazepine, phenobarbital, phenytoin (Dilantin), rifampin	Carvedilol(Coreg), celecoxib (Celebrex), glipizide (Glucotrol), ibuprofen (Motrin), irbesartan (Avapro), losartan (Cozaar)

	Septra)		
CYP2C19	Fluvoxamine, isoniazid (INH),ritonavir	Carbamazepine, phenytoin, rifampin	Omeprazole (Prilosec), phenobarbital,phenytoin
CYP2D6	Amiodarone, cimetidine, diphenhydramine (Benadryl), fluoxetine, paroxetine (Paxil), quinidine,ritonavir, terbinafine (Lamisil)	No significant inducers	Amitriptyline,carvedilol, codeine, donepezil (Aricept), haloperidol (Haldol), metoprolol (Lopressor), paroxetine, risperidone (Risperdal), tramadol (Ultram
CYP3A4 and CYP3A5	Clarithromycin (Biaxin), diltiazem(Cardizem), erythromycin, grapefruit juice, itraconazole (Sporanox), ketoconazole (Nizoral), nefazodone (Serzone‡), ritonavir, telithromycin (Ketek), verapamil (Calan)	Carbamazepine, H ypericum perforatum (St. John's wort), phenobarbital, phenytoin, rifampin	Alprazolam (Xanax), amlodipine (Norvasc), atorvastatin (Lipitor), cyclosporine (Sandimmune),diazepam (Valium), estradiol (Estrace), simvastatin (Zocor), sildenafil (Viagra),verapamil, zolpidem (Ambien)

CYP=Cytochrome P.

Information from references 14, 15,16 and 17

Table 2: Examples of Common Drug-Drug Interactions Involving theCytochrome P450 Enzyme System.

Drug(s)/product	Enzyme inhibitor orinducer	Drug(s)	Metabolizing enzyme	Possible clinical effect
Amiodarone (Cordarone)	CYP2C9 and CYP3A4 inhibitor	Warfarin (Coumadin)	CYP2C9	Increasedrisk of bleeding caused by increased warfarin level[18]
Carbamazepine (Tegretol), phenobarbital, phenytoin (Dilantin)	CYP3A4 inducer	Ethinyl estradiol-containing contraceptives	CYP3A4	Unplannedpregnancy caused by reduced estradiol level[19]
Clarithromycin (Biaxin), erythromycin, telithromycin (Ketek)	CYP3A4 inhibitor	Simvastatin (Zocor), verapamil (Calan)	CYP3A4	Myopathy or rhabdomyoly sis caused by increased simvastatin level[20] Hypotension and QT interval prolongation caused by increased verapamil level[21]
Diltiazem (Cardizem), verapamil	CYP3A4 inhibitor	Prednisone	CYP3A4	Immunosuppression caused by increased prednisoloneserum levels[22]

Fluoxetine(Prozac), paroxetine(Paxil),	CYP2D6 inhibitor	Risperidone (Risperdal), tramadol (Ultram)	CYP2D6	Increased risk of extrapyramidal adverse effects caused by increased risperidone level[23]; decrease in analgesic effect caused by low level of active metabolite[24]
Grapefruit juice	CYP3A4 inhibitor	Buspirone (Buspar)	CYP3A4	Dizziness and serotonin syndrome caused byincreased buspironelevel[25]
Metronidazole (Flagyl)	CYP2C9 inhibitor	Warfarin	CYP2C9	Increasedrisk of bleeding caused by increased warfarin level[26]
Terbinafine (Lamisil)	CYP2D6 inhibitor	Amitriptyline	CYP2D6	Dry mouth, dizziness, and cardiac toxicity caused by prolonged increase in amitriptylineand nortriptyline (Pamelor) levels[27]

CYP=cytochrome P.

Information from references 18 through 27

CONCLUSION

Cytochromes P450 are isoenzyme containing heme act as a cofactor CYP450 so named as they bound to membranes with in cell that oxidise substances using iron involved drug metabolism and detoxification foreign chemicals and found high level in liver It has been estimated that 90% of drug oxidation can be attributed tosix main enzymes: CYP 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 The most significant CYP isoenzymes in terms of quantity are CYP3A4 and CYP2D6. CYP3A4 is foundnot only in the liver but also in the gut wall Although this class has more than 50 enzymes, six of them metabolize 90 percent of drugs, with the two most significant enzymes being CYP3A4 and CYP2D6. Cytochrome p450 enzymes can be inhibited and induced by drugs, resulting in clinically significant drugs- drug interaction Cytochrome P450 enzymes being affected by previous administration of other drugs. After coadministration, some drugs act as potent enzyme inducers, while others are inhibitors. Drug interactions involving the P450 isoforms generally are of two types: enzyme induction or enzyme inhibition. When two drug are co-administered concurrently, substrate for same enzyme second drug clear from the

body withoutshow pharmacological reaction and chances of therapeutic failure in case of induction. Enzyme inhibition reduces metabolism, whereas induction can increase Drug interactions involving the P450 isoforms generally are of two types: enzyme induction or enzyme inhibition. Common substrates, inhibitors and inducers of P450 isozymes. Enzyme inhibition reduces metabolism, whereas induction can increase. The adverse effects can result in more than one way for example, from drug-drug interactions when one drug inhibits the metabolism of another drug increasing the drug to toxic levels.

REFERENCE

1. Vitolo Michele ”brief review on enzyme activity”; World Journal of Pharmaceutical Research, 2019; 9(2): 60-76.
2. Deodhar Malavika; Al Rihani B Sweilem; Arwood J Meghan; Darakjian Lucky; Dow pamela; turgeon Jacques and Michaud Veronique;” Mechanismsof CYP450 Inhibition: Understanding Drug-Drug Interactions Due to Mechanism-Based Inhibition in Clinical Practice”; Parmaceutics, 2020; 12(19): 846.
3. Lynch, T.; Price, A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am. Fam. Physician, 2007; 76: 391–396.
4. Abdel-Rahman, S.M.; Gotschall, R.R.; Kauffman, R.E.; Leeder, J.S.; Kearns, G.L. Investigation of terbinafine as a CYP2D6 inhibitor in vivo. Clin. Pharmacol Ther., 1999; 65: 465–472.
5. Vickers, A.E.M.; Sinclair, J.R.; Zollinger, M.; Heitz, F.; Glänzel, U.; Johanson, L.; Fischer, V. Multiple Cytochrome P-450s Involved in the Metabolism of Terbinafine Suggest a Limited Potential for Drug-Drug Interactions. Drug Metab. Dispos, 1999; 27: 1029–1038.
6. Rasmussen, B.B.; Nielsen, T.L.; Brøsen, K. Fluvoxamine inhibits the CYP2C19-catalysed metabolism of proguanil in vitro. Eur. J. Clin. Pharmacol, 1998; 54: 735–740.
7. Lam, Y.W.; Alfaro, C.L.; Ereshefsky, L.; Miller, M. Pharmacokinetic and pharmacodynamic interactions of oral midazolam with ketoconazole, fluoxetine, fluvoxamine, and nefazodone. J. Clin. Pharmacol, 2003; 43: 1274–1282.
8. Drolet, B.; Khalifa, M.; Daleau, P.; Hamelin, B.A.; Turgeon, J. Block of the rapid component of the delayed rectifier potassium current by the prokinetic agent cisapride underlies drug-related lengthening of the QT interval. Circulation, 1998; 97: 204–210.
9. Naritomi, Y.; Teramura, Y.; Terashita, S.; Kagayama, A. Utility of microtiter plate assays for human cytochrome P450 inhibition studies in drug discovery: Applicationof

simple method for detecting quasi-irreversible and irreversible inhibitors. Drug Metab. Pharmacokinet, 2004; 19: 55–61.

10. Uttamsingh, V.; Gallegos, R.; Liu, J.F.; Harbeson, S.L.; Bridson, G.W.; Cheng, C.; Wells, D.S.; Graham, P.B.; Zelle, R.; Tung, R. Altering Metabolic Profiles of Drugsby Precision Deuteration: Reducing Mechanism-Based Inhibition of CYP2D6 by Paroxetine. J. Pharmacol. Exp. Ther., 2015; 354: 43–54.
11. Bertelsen, K.M.; Venkatakrishnan, K.; Von Moltke, L.L.; Obach, R.S.; Greenblatt, D.J. Apparent mechanism-based inhibition of human CYP2D6 in vitro by paroxetine: Comparison with fluoxetine and quinidine. Drug Metab. Dispos, 2003; 31: 89–293.
12. Kouladjian, L.; Chen, T.F.; Gnjidic, D.; Hilmer, S.N. Education and Assessment of Pharmacists on the Use of the Drug Burden Index in Older Adults Using a Continuing Professional Development Education Method. Am. J. Pharm. Educ, 2016; 80: 63.
13. Ogilvie, B.W. An In Vitro Investigation into the Mechanism of the Clinically Relevant Drug-Drug Interaction between Omeprazole or Esomeprazole and Clopidogrel. Ph.D. Thesis, University of Kansas, Lawrence, KS, USA, 23 April 2015.
14. Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. Pharmacotherapy, 1998; 18: 84-112.
15. Cozza KL, Armstrong SC, Oesterheld JR. Drug interactions by medical specialty. In: Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-Glycoproteins. 2nd ed. Washington, D.C.: American Psychiatric Pub., 2003; 167–396.
16. Lexi-Comp [online reference library]. Hudson, Ohio: American Pharmaceutical Association; 1978. Updated daily. Accessed February, 21, 2007, at: http://www.crlonline.com/crlsql (subscription required).
17. Indiana University School of Medicine. P450 drug interactions table. Accessed February 21, 2007, at: http://medicine.iupui.edu/flockhart/table.htm.
18. Heimark LD, Wienkers L, Kunze K, Gibaldi M, Eddy AC, Trager WF, et al. The mechanism of the interaction between amiodarone and warfarin in humans. Clin Pharmacol Ther., 1992; 51: 398-407.
19. Crawford P, Chadwick DJ, Martin C, Tjia J, Back DJ, Orme M. The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids. Br J Clin Pharmacol, 1990; 30: 892-6.
20. Molden E, Andersson KS. Simvastatin-associated rhab-domyolysis after co administration of macrolide antibiotics in two patients. Pharmacotherapy, 2007; 27:

603-7.

21. Goldschmidt N, Azaz-Livshits T, Gotsman null, Nir-Paz R, Ben-Yehuda A, Muszkat M. Compound cardiac toxicity of oral erythromycin and verapamil. Ann Pharmacother, 2001; 35: 1396-9.
22. Imani S, Jusko WJ, Steiner R. Diltiazem retards the metabolism of oral prednisone with effects on T-cell markers. Pediatr Transplant, 1999; 3: 126-30.
23. Spina E, Avenoso A, Scordo MG, Ancione M, Madia A, Gatti G, et al. Inhibition of risperidone metabolism by fluoxetine in patients with schizophrenia: a clinically relevant pharmacokinetic drug interaction. J Clin Psychopharmacol, 2002; 22: 419-23.
24. Laugesen S, Enggaard TP, Pedersen RS, Sindrup SH, Brosen K. Paroxetine, a cytochrome P450 2D6 inhibitor, diminishes the stereoselectiveO-demethylation and reduces the hypoalgesic effect of tramadol. Clin Pharmacol Ther., 2005; 77: 312-23.
25. Lilja JJ, Kivisto KT, Backman JT, Lamberg TS, Neuvonen PJ. Grapefruit juice substantially increases plasma concentrations of buspirone. Clin Pharmacol Ther., 1998; 64: 655-60.
26. Kazmier FJ. A significant interaction between metronidazole and warfarin. Mayo Clin Proc., 1976; 51: 782-4.
27. Castberg I, Helle J, Aamo TO. Prolonged pharmacokinetic drug interaction between terbinafine and amitriptyline. Ther Drug Monitor, 2005; 27: 680-2.