Peertechz

CHEMISTRY GROUP

OPEN JOURNAL OF Chemistry

ISSN: 2641-3051 DOI: https://dx.doi.org/10.17352/ojc

Srinivas Maddi[1]*, Thirumaleswara Goud[2] and Pratima Srivastava[1]

[1]GVK Biosciences PVT LTD, Nacharam, Hyderabad, 500076, India
[2]Creative Educational Society's College of Pharmacy., Chinnatekur, Kurnool, Andhra Pradesh, India

Dates: Received: 23 June, 2017; **Accepted:** 10 July, 2017; **Published:** 11 July, 2017

***Corresponding author:** Srinivas Maddi, Associate Director, DMPK Biology Division, 28A IDA Nacharam, Hyderabad 500076, Telangana, India, Tel: 919701166299; E-mail: srinivasarao.maddi@gvkbio.com

Keywords: Drug metabolizing enzymes; Drug transporters; Drug-drug interactions

https://www.peertechz.com

Review Article

Cytochrome P450 Enzymes, Drug Transporters and their Role in Pharmacokinetic Drug-Drug Interactions of Xenobiotics: A Comprehensive Review

Abstract

Drug-Drug interactions (DDI) is a serious clinical issue. An important mechanism underlying of DDI, is induction or inhibition of drug metabolizing enzymes (DMEs) and transporters that mediate metabolism, cellular uptake and efflux of xenobiotics. DDI cannot be avoided in many cases, as they belong to routine medical practice. Especially DMEs and transporters of small intestine, liver, kidney are the major determinants of the pharmacokinetic profile of drugs. Enzymes and transporters mediated DDI in these three organs can considerably influence the pharmacokinetics and clinical effects of drugs. The purpose this review is to elucidate the effect of cytochrome P-450 (CYP 450) enzymes and transporters mediated DDI on the pharmacokinetics and further its clinical implications.

Introduction

Modification of a patient's clinical response to the administered drug by the co-administration of another drug is defined as a Drug-Drug Interaction (DDI). Without affecting the drug kinetics, when a pharmacological response is changed either through agonism or antagonism, those DDIs are termed as pharmacodynamic interactions. When we observe the alterations in drug disposition mainly via induction or inhibition of transporters or metabolic enzymes and drug transporters involved in drug absorption, distribution, metabolism or excretion, those DDIs are termed as pharmacokinetic interactions [1].

Pharmacokinetic DDIs are responsible for approximately 20-30% of the adverse drug reactions in general population, they also account for about 10% of the cases under emergency department and contribute 3-5% of the medication errors in hospitalized patients [2,3]. Since the drug pharmacokinetics can be significantly altered by both transporters and enzyme mediated DDIs, it can potentially affect the therapeutic efficacy or toxicity of drugs [4]. DDIs based on metabolism are specifically due to induction and/or inhibition of cytochrome P450 (CYP 450), they have been considered to be the most dangerous ones [5]. Based on the pharmacological and toxicological effects of both the parent drug and its metabolites, the clinical consequences of CYP induction or inhibition depends and if the victim drug has a narrow therapeutic index this may be particularly significant because DDIs based on metabolism may cause changes in the concentration of drug up to 10 fold whose biotransformation is induced or inhibited [6]. This is particularly significant if the parent is responsible for the pharmacological effect and the affected metabolic pathway constitutes its main route of elimination, induction and inhibition may cause potential toxic effects or complete loss of therapeutic efficacy, respectively. Vice versa, if the parent compound is a prodrug, enzyme induction likely may result in potential toxic effects whereas, inhibition of its metabolic conversion may cause a reduction in therapeutic efficacy. When reactive metabolites are generated, induction may be dangerous as they can cause serious idiosyncratic reactions frequently [7]. A recent systematic review revealed that, based on in vitro tests performed at the time of drug development, majority of the new molecular entities have been observed to be perpetrators of metabolic interactions. It has been found that 45% of the new molecular entities are the victims of clinically significant metabolic DDIs [8]. Due to enzyme induction or inhibition it is very difficult to manage the wide inter individual variability in the magnitude of drug interactions by dose adjustment [9]. By the FDA regulatory guidance, more complex and refined predictive models have been proposed and endorsed

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006

subsequently. Recently, it has been pointed out that they do not enhance predictive capacity. The underlying mechanism that alters the drug disposition in liver disease is unknown and hence it is difficult to predict the effect of liver insufficiency on metabolism based DDIs [10,11].

Drug Metabolizing Enzymes (DMEs)

For metabolizing a vast array of xenobiotic compounds which includes drugs, endogenous compounds and environmental pollutants, DMEs are very much essential, which are a diverse group of proteins. An important area of research that impacts on basic enzymology, pharmacology and toxicology is the understanding of the structure activity relationships for the DMEs and their substrates. In this perspective, utilization of recombinant DMEs play a significant role.

Drug metabolizing enzymes can be categorized into two groups.

Oxidative DMEs

i. Cytochrome P 450 (CYP 450)

ii. Flavin mono oxygenases (FMOs)

Conjugative DMEs

i. UDP-glycosyl transferases (UGTs)

ii. Glutathione transferases (GSTs)

iii. Sulfo transferases (SULTs)

iv. N-acetyl transferases (NATs) [12,13]

Oxidative Drug Metabolizing Enzymes

Cytochrome P 450

The initial step in the biotransformation of xenobiotic compounds is catalyzed by the CYP450 enzymes in the liver. These enzymes are members of mixed function oxidase family. They catalyze and introduce an oxygen atom into substrate molecules which often results in dealkylated and hydroxylated metabolites. In humans, more than fifty CYP450 isoenzymes are known to exist. Based on the similarities of amino acid sequence they are classified into 17 families and 39 sub families. At the amino acid level, proteins from the same family have greater than 40% similarity, whereas in the same sub families have greater than 55% homology [14]. According to the standard nomenclature, the family is designated by a number followed by a letter which designates the sub family and a second number which designates the sub family's individual members. Majorly, the drug metabolism can be carried out by the CYP1, 2 and 3 families and occurs mainly in the liver. In our body, the highest concentration of CYP450 is observed in liver. The significance of extra hepatic metabolism in tissues like lung and intestine however is also recognized. The adult human liver comprises of the following isozymes that include 1A2, 2A6, and 2B6 the 2C sub family-(2C8, 2C9, 2C18 and 2C19), 2D6, 2E1 and the 3A subfamily (3A4 and 3A5) [12-15]. The process of oxidation of organic molecules by P450 is complex and the overall reaction can be represented by the following equation [16].

$$RH + O_2 + NADPH + H^+ \rightarrow ROH + H_2O + NADP^+$$

The isolation of CYP 450 is difficult and tedious. The utility of the protein for in vitro metabolism studies have been greatly enhanced by the methods like heterologous expression of recombinant CYP 450 using Baculovirus (BaV) and E.coli [17].

Flavin mono oxygenases (FMOs)

FMOS are associated with the endoplasmic reticulum and catalyze the oxidation of organic compounds using NADPH and molecular oxygen as the source of electrons resulting in the decrease of one of the oxygen atoms. FMOs are similar to CYP450 enzymes but they are mechanistically distinct from the CYP450s, in that they react with NADPH and oxygen in the absence of substrate to form a 4α-hydro peroxy flavin enzyme intermediate. In the cell, FMOs exist in an activated form. Their interaction with a nucleophilic group like phosphate, amine or thiol is necessary for the completion of the catalytic cycle. In human liver, FMO_3 is present in most abundant form and in terms of overall drug metabolism it is believed to be the dominant member [18,19].

Conjugative Drug Metabolizing Enzymes

UDP glycosyl transferase (UGTs)

By using UDP-glucuronic acid as a donor molecule, UGT catalyzes the glucuronidation of xenobiotics at hydroxyl, sulfhydryl, imino, amino and carboxyl groups. Usually, this generates products which are more hydrophilic. Hence, they are readily excreted in urine or bile.

UDP-glucuronic acid + R → UDP + R-glucuronide

Generally, glucuronidation is classified as Phase-II metabolism. It is the phase that occurs after CYP450 dependent oxidative metabolism. Majority of the compounds need not require prior oxidation because they have functional groups already that can be glucuronidated. Glucuronidation of 5- lipoxygenase inhibitors and UGT2B7 dependent glucuronidation of morphine are the examples of first pass metabolism catalyzed by UGTs. UGTs are located in the lumen of the endoplasmic reticulum. In human two UGT families have been identified that includes UGT1 and UGT2. In human liver, the members of the UGT1 family are expressed in which most of the xenobiotic metabolism takes place which includes UGT1A1, 1A3, 1A4, 1A6 and 1A9 [20-22].

Glutathione transferases (GSTs)

The formation of thio ether conjugates between glutathione and reactive xenobiotics by directly adding or displacing an electron withdrawing group can be catalyzed by GSTs.

GSH + R → GS-R (addition)

GSH + R-X → GS-R + HX (displacement of an electron withdrawing group)

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006

The major biological function of GST is to provide defense against electrophilic chemical species. Most of the GSTs are cytosolic homo dimers. They were composed of about 25k Da subunits from one of four structural classes. (1) Alpha [α], (2) Mu [μ], (3) Pi [π] and (4) Theta [θ]. To some tissues in mammals which include lungs, liver, kidney and intestine, α isoform (GSTA1-1) is restricted. The μ isoform (GSTM1-1) is present in liver and also in some other tissues. Throughout the body except in the liver, the π isoform (GST P1-1) is extensively distributed. In majority of the tumor cells GSTP1-1 is abundant.

Sulfo transferase (SULTs)

The conjugation of sulfate groups on to a variety of xenobiotic and endogenous substrates that have the acceptor moieties like hydroxyl and amine groups can be catalyzed by SULT enzymes.

$$R\text{-}XH + PAPS \rightarrow R\text{-}SO_4 + \text{Phospho adenosine} + H^+$$

For sulfonation by these enzymes, the cofactor 3'-phosphoadenosine 5' phospho sulfate (PAPS) is essential. Usually, sulfonation causes molecules to lose their biological activity. With different biochemical properties, several SULT enzymes have been characterized in human and animal tissue. In tissues, two general classes exist. (1) Cytosolic enzymes, (2) membrane bound enzymes. The cytosolic enzymes have a significant role in drug metabolism, whereas the membrane bound enzymes have a significant role in the sulfonation of glycoproteins and glycosaminoglycan. In humans there are currently 10 known SULTs. Among them five are expressed to be in adult liver that includes SULT1A1, SULT1A2, SULT1A3, SULT1E and SULT2A1. SULT enzymes with allelic variants do exist and studying their functional role and frequency in drug disposition is a very interested area of research [23-26].

N-acetyl transferase (NATs)

The biotransformation of hydrazine and aromatic amines to the respective hydrazides and amides can be catalyzed by N-acetyl transferases (NAT) by using acetyl co enzyme A as a donor. The O-acetylation of N-hydroxy aromatic amines to acetoxy esters can also be catalyzed by them .

$$R\text{-}NH_2 + COA\text{-}S\text{-}COCH_3 \rightarrow R\text{-}NCOCH_3 + COA\text{-}SH$$

$$R\text{-}NHOH + COA\text{-}S\text{-}COCH_3 \rightarrow R\text{-}NHOCOCH_3 + COA\text{-}SH$$

In humans, there are two NAT isoforms that includes NAT1 and NAT2. NAT1 is expressed in liver and many other tissues, whereas NAT2 is expressed only in the gut and liver [27]

In the metabolism of a wide variety of both exogenous and endogenous compounds CYP 450 enzymes are involved that constitute a large family of heme-thiolate protein [28]. In the year 1955, CYP 450 enzymes were first discovered in rat liver microsomes. In the presence of carbon monoxide, they are characterized by an intense absorption band at 450nm [29]. On the smooth endoplasmic reticulum, the CYP 450 mixed function mono oxygenases are located throughout the body; small intestine and liver are the major sites [30]. For a wide range of compounds, these enzymes are responsible for the oxidative (Phase -1) metabolism. Lipophilic drugs can be biotransformed to more polar compounds that can be excreted by the kidneys. In some instances the metabolites can be toxic, teratogenic and even carcinogenic. In human, approximately 12 CYP 450 gene families have been identified. In majority of the drug biotransformation, three families are mainly involved that includes CYP 450 1, 2 and 3 (CYP-1, CYP-2and CYP-3). In the adult liver, the major form of CYP 450 is the CYP3A4 which metabolize the larger proportion of drugs. CYP 3A4 and CYP 3A3 cannot be distinguished from each other because they have more similarities in metabolizing the substrates. In stomach, the major enzyme is the CYP 3A5 and is present in only 20-30% of the Caucasians. The deficiency in CYP 3A5 does not cause any problem because all the major functions can be carried out CYP 3A4. Induction and inhibition of CYP 450 enzymes are the most common causes of altered drug biotransformation reactions [31-33].

Drug-Drug Interactions Mediates Through CYP Induction

Enzyme induction is a process, in which a drug stimulates a particular isoform of CYP450, and there occurs a gene mediated increase in number of molecules of the DME. Drug that stimulates the enzyme is termed as an "inducer". Induction is a complex, dose related phenomenon requiring the inducer to reach a critical concentration to bind and activate transcription factors at an intranuclear receptor or regulation point, from which up regulation of messenger RNA occurs with subsequent increase in protein production. Induction is a relatively slow process that may start after 3-4 days of exposure to an inducer. Maximal effect usually occurs after 7-10 days and requires an equal or longer time to dissipate after inducer is stopped.

Increased synthesis of enzyme which is associated with exposure to drugs is called as induction. When a drug stimulates the biotransformation of co-administrated drugs, the induction can occur. This may occur through the same enzyme pathway or via an alternative pathway. For a given CYP 450 family, specific inducers are usually present. In addition to other agents, sometimes a drug can induce its own biotransformation. Within the first two days of treatment, effects of induction can be seen. For the synthesis of new enzyme, it usually takes more than one week. Half-life of enzyme production and degradation and plasma concentration of the inducer are related with the time course of enzyme induction onset and offset (Figure 1).

Inducers are classified on the basis of percent decrease in plasma area under curve (AUC) values of substrate drug. Strong inducers are those which produce 80% or more decrease in AUC of substrate. Examples of strong inducers of CYP3A4 include Rifampin, Phenytoin, Carbamazepine and St. John's wort. Moderate inducers produce between 50% and 80% decrease in AUC of substrate and include Phenobarbitone, Nevirapine and Efavirenz. Weak inducers produce between 20% and 50% decrease in AUC substrate. Induction-based interactions can lead to significant manifestations. Induction of estrogen metabolism may lead to failure of contraceptive effect and

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006

unexpected pregnancy. Similarly, therapeutic failure with digoxin and digitoxin is known. Failure of immunosuppressive action of Cyclosporine can lead to organ transplant rejection. Patients receiving enzyme inducers may show failure of therapy to antimicrobial agents like Metronidazole or Doxycycline prescribed for some infections. Antiepileptic drug doses may fall short and seizures may be precipitated. Loss of anticoagulant effect of Warfarin is known to lead to thrombosis. When the induction wanes, failure to recognize the need to reduce the Warfarin dose may lead to bleeding. Methadone withdrawal reactions are known in patients on opioid substitution programmes, who receive inducers for another purpose.

Drug - Drug Interactions Mediates Through CYP Inhibition

Enzyme inhibition is a phenomenon in which some particular drugs produce inhibition of enzyme responsible for breakdown of certain substrates. Drugs which cause inhibition called enzyme inhibitors. Enzyme inhibition is a direct phenomenon of affecting a particular enzyme. Therefore inhibition is often a fairly rapid process and may begin as soon as sufficient tissue concentration of inhibitor is achieved. Various mechanism involved in inhibition of metabolism include competition and reversible binding to enzyme (Quinidine), inactive complex formation with enzyme (macrolides), enzyme destruction (Vinyl chloride), inhibition of synthesis of enzyme molecules of particular isoform or competing for the same isoform.

The most common mechanism of inhibition is the competitive inhibition that occurs when 2 or more drugs compete for the same enzyme. The clinical significance of an inhibition interaction depends primarily on the drug's relative concentration and also on various patient specific factors. Drugs can bind with heme–binding site reversibly or irreversibly. This inhibits the binding of other drugs. By the CYP 450 system, some drugs undergo metabolic activation. Stable complexes with CYP 450 can be generated by the metabolites so that the cytochrome is held in an inactive state. Since it is relatively long in duration, there can be great clinical significance to this interaction. There is a chance of toxicity, when the interaction involves narrow therapeutic drugs. Usually, enzyme inhibition begins with the first dose of the inhibitor. When the inhibitor reaches steady state, inhibition is found to be maximal and when the inhibited drug reaches steady state at its new, longer half-life the maximum concentration of the inhibited drug occurs. Similarly, the time which is necessary for the interaction to resolve also depends on the half –lives of the involved drugs [34] (Figure 2).

Inhibitors are classified as strong, moderate, or weak depending upon their effect on the substrate. Strong inhibitor is the one that causes more than 5-fold increase in plasma AUC values or more than 80% decrease in substrate clearance. Some examples of strong inhibitors and the isoform inhibited are Fluconazole (2C9), Gemfibrozil (2C8), Fluvoxamine and Ciprofloxacin (1A2), Quinidine and Fluoxetine (2D6) Indinavir, Ritonavir and Ketoconazole (3A4, 5 and 7).

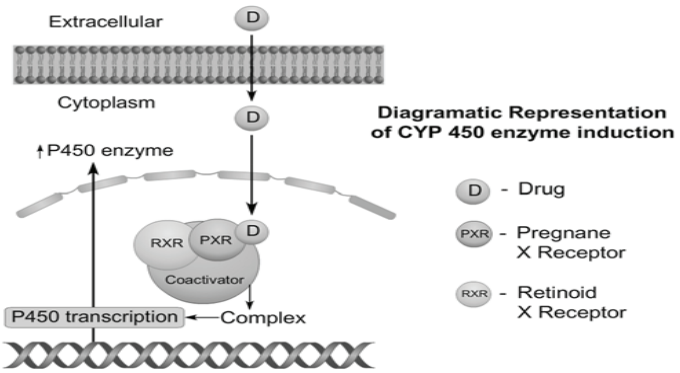

Figure 1:

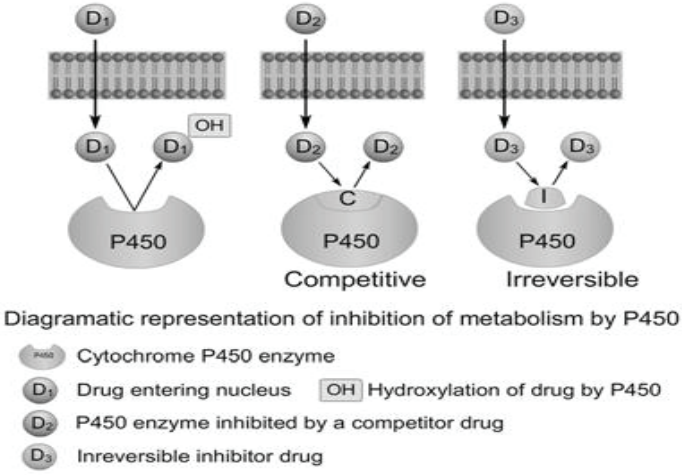

Figure 2:

Moderate inhibitor causes more than 2-fold increase in plasma AUC values or 50-80% decrease in clearance of substrate. Examples of moderate inhibitors with the isoform they inhibit are Trimethoprim (2C8), Amiodarone (2C9), Duloxetine, Sertraline and Terbinafine (all 2D6), Erythromycin, Fluconazole, Verapamil and Diltiazem (all 3A4, 5, 7). Weak inhibitor causes 2-fold increase in plasma AUC values or 20-50-% decrease in clearance. Cimetidine is a weak inhibitor at 1A2, 3A4 and 2D6. Amidarone is a weak inhibitor at 2D6. The following table listed the important drug-drug interaction related CYP enzymes including corresponding substrates and inhibitors (Table 1).

Cytochrome P450 Mediated Drug-Drug Interactions In Hepatic Dysfunction

In the pathogenesis of various liver diseases, the hepatic CYPs are involved. Hepatotoxicity can be induced by CYP mediated activation of drugs to toxic metabolites (e.g.: Halothane and Acetaminophen). In some cases, covalent binding of the toxic metabolite to CYP leads to immune mediated hepatotoxicity and anti–CYP antibodies. In the serum of patients with type II auto immune hepatitis, anti- CYP 2D6 antibodies are present.

The mechanism and the pathogenic significance remain unclear. Various studies revealed the role of CYP2E1 in the pathogenesis of non-alcoholic steatohepatitis and alcoholic

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006

Table 1:

CYP Isoform	Substrates	Inhibitor
3A4	Midazolam	Ketoconazole
2D6	Dextromethorphan	Quinidine
1A2	Tacrine	Alphanaphthaflavone
2C9	Diclofenac	Sulfaphenazole
2C19	S-Mephenytoin	N-3-Benzyl nirvanol
2B6	Buproprion HCL	Ticlopidine
2C8	Paclitaxel	Quercetine
2E1	Chlorozoxazone	4-Methyl pyrazole

liver disease. Increased CYP2E1 activity is associated with lipid peroxidation and the production of reactive oxygen species with secondary damage to mitochondria and cellular membranes can be seen in these conditions. It has also been postulated that CYP2E1 has a role as a cofactor for hepatocellular carcinoma due to its ability to activate carcinogens. Particularly for the drugs mediated by CYPs, drug metabolism can be impaired in patients with liver disease.

The activity and content of CYP1A, 2C19 and 3A seems to be more vulnerable to the effect of liver disease whereas CYP2C9, 2D6 and 2E1 are less affected. Based on the etiology of liver disease, the pattern of CYPs isoenzymes alternations also varies. It has been demonstrated that a strong relationship was observed between the activity of CYPs and the cirrhosis severity. To assess the hepatic functional reserve, the usefulness of measuring CYP activity remains uncertain [35].

Effect of hepatic dysfunction on enzyme Inhibition

In hepatic dysfunction, five types of factors can affect the extent of inhibitory DDIs.

1. Reduced enzyme content.
2. Hepatic extraction ratio of the drug with inhibited metabolism.
3. Reduced liver uptake of the inhibitor.
4. Nature of the inhibitory interaction (reversible or irreversible).
5. Plasma protein binding of the drug with inhibited biotransformation.

Reduced enzyme content

In hepatic dysfunction, the expression of various CYP enzymes has been shown to be markedly decreased especially, CYP1A2 and CYP3A4. Decreased enzyme content results in reduced inhibitory effect [36, 37].

Hepatic extraction ratio of the drug with inhibited metabolism

The hepatic clearance of drugs with a low extraction ratio is decreased in proportion to the degree of enzyme inhibition, as to the clearance of these drugs depends on the metabolic capacity of the liver. The clearance of drugs with a high extraction ratio can be determined by liver perfusion and should be unaffected by a reduction in intrinsic clearance caused by enzyme inhibition [38].

Reduced liver uptake of the inhibitor

For various basic drugs which are structurally unrelated, decreased drug uptake by the cirrhotic liver has been observed by the in vitro studies [39].

Nature of the inhibitory interaction (reversible or irreversible)

Liver dysfunction may differentially affect the accumulation kinetics in the liver cell of reversible and irreversible inhibitors. In between the intra and extra cellular spaces, reversibly binding molecules rapidly equilibrate whereas the binding of irreversible inhibitors is time-dependent and if the inhibitor concentration exceeds that of the enzymatic protein it can precede up to total enzyme inhibition.

Plasma protein binding of the drug with inhibited biotransformation

Displacement influences the magnitude of inhibitory DDIs because when the perpetrator of an interaction inhibits the metabolism and causes displacement of the victim drug from its plasma protein-binding sites [40]. The reduction in plasma protein concentration associated with hepatic dysfunction enhances the magnitude of drug interactions consequent to plasma protein-binding displacement. The consequences of enzyme inhibition are masked by the displacement, the effect on the total plasma clearance of the victim drug by any perpetrator causing plasma protein binding displacement and metabolic inhibition may reduce with the increase in liver dysfunction. Up to the hardly predictable levels, the free concentration of the victim drug tend to increase [41].

CYP 450 Mediated Drug-Drug Interactions in Diabetes Mellitus

The incidence of altered biotransformation and bioavailability of the orally administered drugs may be increased by any change in the cytochrome P450 enzymes metabolizing capacity in the liver and intestine. The changes in the CYP 450 and FMO expression and function in the liver and intestine can occur by Insulin dependent diabetes mellitus (IDDM). The metabolism in IDDM mediated by CYP and FMO was investigated by streptozotocin (STZ) induced experimental diabetes model. Due to the hormonal and metabolic changes associated with diabetic state usually the alterations of cytochrome P450 enzyme system takes place in both the organs.

In the regulation of these enzymes insulin plays a crucial role either directly or indirectly via insulin signaling pathway because, majority of the alterations are either completely or partially restored following treatment with insulin. In experimental diabetes, CYP2C11 and CYP2C13 are down regulated. In diabetes, alterations of CYP2C22 and CYP2C23 are less reported; also the effect of altered CYP mediated

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006

metabolism on newly developed drugs or clinically used drugs is less investigated. Screening of drug safety plays a significant role in the process of drug research and development [42,43].

Drug-Drug Interactions Via Non Microsomal Enzyme Inhibition (Other than CYP 450)

Non-microsomal enzymes may be inhibited by certain agents to produce significant drug interactions. Allopurinol is a xanthine oxidase inhibitor, used in gout to decrease the uric acid synthesis. The anticancer drugs, Mercaptopurine or Azathioprine are also metabolized by the same enzyme. So if Allopurinol is used concurrently with any of the two, their breakdown is inhibited, and their action is potentiated. Failure to recognize this interaction may lead to their toxic effect. On the other hand, this knowledge can benefit in a way that one could decrease the doses of Mercaptopurine or Azathioprine while giving them concurrently with allopurinol. Carbidopa is a peripheral dopa decarboxylase inhibitor. It inhibits peripheral breakdown of Levodopa, which allows more of Levodopa to reach the brain, and also reduces the risk of its peripheral adverse effects. MAO inhibitors when given with amphetamine or foods containing tyrosine/turamine/tryptophan or any other indirectly acting amines, inhibit the breakdown of these amines. These amines escape degradation and enter systemic circulation where they tend to release norepinephrine at nerve endings leading hypertensive crisis. Cilastatine is combined with Imipenem to prevent degradation of Imipenem at renal tubular cells as Cilastatin inhibits the enzyme renal dehydropeptidase responsible for Imipenem degradation. This potentiates the action of Imipenem. In addition, because Imipenem metabolite is responsible for renal toxicity of Imipenem and Cilastatin is preventing the breakdown, renal toxicity of Imipenem can be minimized.

Drug-Drug Interactions Via First Pass Metabolism

Drug interactions sometimes depend on extent of first pass metabolism of drugs. Oral bioavailability of a drug is likely to be increased if its first pass metabolism is inhibited by another drug given concurrently that competes with it for first pass metabolism. Propranolol increases bioavailability of chlorpromazine by decreasing its first pass metabolism. Propranolol decreases breakdown of lidocaine by decreasing hepatic blood flow, because Lidocaine metabolism depends on the hepatic blood flow.

Drug Transporters

A vast number of membrane transport proteins have been found during the last two decades. In the absorption, distribution and elimination of drugs, these transporters are the significant determinants. Before the first transporter was cloned, the involvement of carriers mediated processes in the drug excretion was already appreciated. In case of drug absorption and tissue uptake, it has become increasingly apparent that transporters play a vital role. Drug transport proteins can be categorized into two major classes that include solute carriers (SLC) and ATP –Binding Cassette (ABC) transporters. From the human genome around 380 unique SLC sequences have been obtained which can be further divided into 48 sub families [44]. The xenobiotics transport activities for around 19 of these gene families were described. These transporters include organic anion transporting polypeptide (OATP), oligopeptide transporter, organic anion/cation/zwitter ion transporter and organic cation transporter (OCT).

For ABC transporter gene, around seven sub families were identified, encoding for 49 different proteins [45, 46]. In particular, transporters belonging to the ABCB, ABCC and ABCG sub families, have specificities of drugs [47]. In the transport of a wide range of substrates, SLC and ABC transporters are involved and they share a wide distribution in the body [48]. A specific drug may interact with a set of membrane transporters at a particular point of the disposition in the body. Based on the direction, transporter can be categorized into influx or efflux transporters by which carries protein translocate the substrate across the cell membrane. By definition itself ABC transporters are efflux transporters. The reason can be explained in such a way that the ABC transporters utilize energy derived from ATP hydrolysis to mediate the primary active export of drugs from the intracellular to the extracellular mileu, often against a steep diffusion gradient. The cellular uptake or influx of substrates was facilitated by majority of the SLC family members. Depending on the concentration gradients of substrate and coupled ion across the membrane some of the SLC transporters exhibit efflux properties. For determining the direction and extent of drug movement in organs like, intestine and kidneys, it is very much important in understanding the interplay between the transporters located on apical and basolateral membrane in epithelial cell [49, 50].

When a drug is orally administrated and dissolved, it crosses the intestinal wall and reaches the liver via portal blood flow which then enters into the systematic circulation and finally getting distributed to the various tissues of the body [51]. A drug molecule passes through several biological membranes during the pharmacokinetic processes. Drug size, lipophilicity and charge are some of the physicochemical properties of the drug that generally affect the extent of drug movement through these membranes. In preventing or facilitating the drug movement, membrane transporters have a vital role. For the sequential traverse of the basolateral and apical membrane, interplay of influx and efflux transporters along with phase -1 and phase-2 metabolisms are required. For example, an uptake transporter like organic anion transporting polypeptide 1B1 (OATP 1B1) may extract its drug substrates into hepatocytes in the liver from the portal blood [52].

In the efflux of the metabolite form the hepatocyte, other drug transporters like multidrug resistance protein 1 (P-glycoprotein) may be important after metabolism. Hence, drug transporters can be regarded as completing the phase-1 and phase-2 enzymes based detoxification systems. Drug uptake delivers the drug to the detoxification system to facilitate metabolism, whereas drug efflux decreases the load on detoxification enzymes (Figure 3).

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006

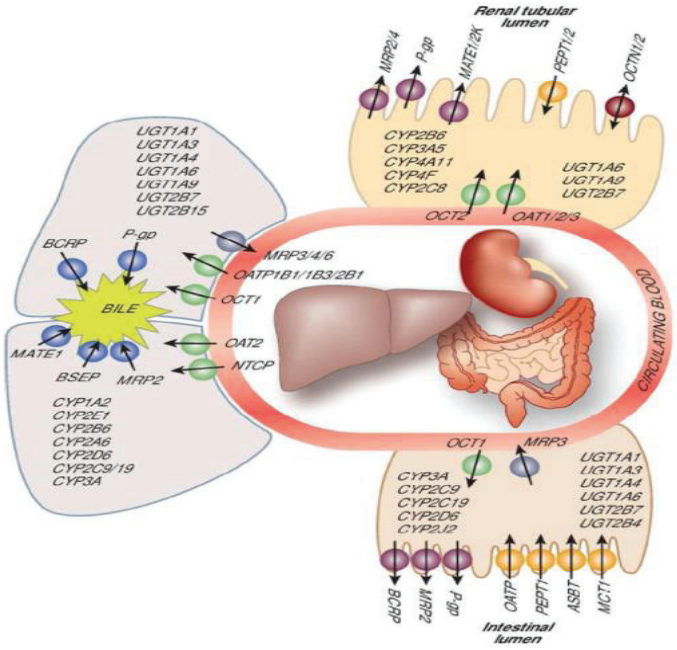

Figure 3:

Organic anion transporting polypeptides (OATPS)

Cellular uptake of various endogenous compounds and clinically significant drugs can be regulated by OATPs. They are membrane influx transporters OATP1A2 was the first discovered human member of the OATP/oatp family. It was cloned by an ortholog of rat oatp1a1. OATPs are designated by Arabic numbering (e.g. OATP1) and within the same family share ≥ 40% amino acid sequence identity. Individual sub families are designated by letters (e.g. OATP 1). Within the same sub family individual gene products are designated by additional Arabic numbers (e.g. OATP 1 B1). The human OATP family comprises of 11 members that include OATP 1A2, 1B1, 1B3, 1C1, 2A1, 2B1, 3A1, 4A1, 4C1, 5A1 and 6A1. In drug pharmacokinetics, the roles of OATP 1B1, 1A2, 1B2 and 2B1 are best characterized. Through the duodenal wall into circulation OATP 1A2 may facilitate the entry of its substrates. On the sinusoidal membrane of human hepatocytes OATP 1B1, 1B3 and 2B1 are located. They mediate the influx of their substrates into the hepatocytes from the blood and hence, it is a significant step preceding elimination of drugs by metabolism or biliary excretion.

All OATPs share an identical transmembrane domain organization with a large fifth extra cellular loop and 12 predicted transmembrane domain as per a computer based hydropathy analysis. The transport of all OATPs/oats occurs through a central, positively charged pore in a so called rocker-switch type of mechanism based on a comparative analysis of OATPs from multiple species. However, OATPs/oatps exact transport mechanism has not been established.

By the gene of the SLCO family, OATPs are encoded. In the short arm of chromosome 12, the gene encoding human OATP1 family members are located where as in the chromosomes 3,5,8,11,15 and 20 the other OATPs are located. In SLCO gene, a lot of sequence variations like single nucleotide polymorphism have been observed. On drug pharmacokinetics, these polymorphisms may lead to significant consequences like reducing the uptake activity of the corresponding OATP. It is evident that significant DDI may result from inhibition and also probably from induction of transporter function. It is challenging for us to predict the role of a single transporter in DDI.

OATP 1B1: OATP 1B1 was previously called as OATP 2, OATP-C and LST-1. In human hepatocytes, it is mainly expressed on the sinusoidal membrane. In the enterocytes of small intestine, SLCO 1B1 MRNA has been detected. Both unconjugated and conjugated bilirubin are transported by in vitro, OATP 1B1. Bile acids (cholate and taurocholate), conjugated steroids (estradiol-17 β-glucuronide, estrone-3-sulfate and dehydro epiandrosterone-3-sulfate) thyroid hormones (triiodothyronine and thyroxine) and eicosanoids (leukotrienes C4 andE4, Prostaglandins E2 and thromboxane B2) are the other endogenous OATP 1B1 substrates. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and HMG-COA reductase inhibitors or statins are some of the examples of OATP 1B1 drug substrates.

OATP1A2: OATP1A2 was previously called as OATP-A. It is expressed in various tissues like brain, liver, intestine and kidneys. According to a study, no detectable levels of SLCO 1A2 MRNA in the duodenum were found. Bile acids, steroid hormones and thyroid hormones are the endogenous substrates of OATP 1A2. A decrease in vitro transport activity towards the OATP 1A2 substrate estrone-3-sulfate was shown by some SLCO 1A2 (encoding OATP1A2) SNPs. In humans, the significance of these findings was unknown.

OATP1B3: OATP1B3 was previously known as OATP8 and LST-2. Based on the sequence homology to the OATP1B1, OATP1B3 was cloned and is mainly expressed on the sinusoidal membrane of human hepatocytes. Bilirubin, conjugated steroids, bile acids, thyroid hormones and eicosanoids are the endogenous substrates of OATP1B3. The OATP1B3 drug substrates overlap with those of OATP1B1. The only hepatic OATP seems to transport Digoxin, Paclitaxel and Docetaxel is OATP1B3.

OATP2B1: OATP2B1 was previously known as OATP-B. It is expressed in the liver at the sinusoidal membrane of hepatocytes and also in other tissues for example heart and intestine. Estrone -3-Sulfate, prostaglandin E2 and de hydroepiandrosterone-3-sulfate are the endogenous substrates of OATP2B1. No data is currently available on the clinical relevance of SLCO2B1 polymorphism. But, few SLCO2B1 sequence variations have been associated with altered transport activity of the protein invitro.

Other OATPs: OATP1C1 was previously called as OATP-F. It is expressed in the human testis, brain and ciliary body and shows a high affinity for thyroid hormones. OATP2A1 acts as a prostaglandin transporter and is widely expressed in various tissues. No drugs have been identified as its substrates currently. OATP3A1 can be expressed in two splice variants that includes a shorter variant and longer variant. The shorter

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006

variant appears to be expressed only in the brain and testis whereas the longer variant is expressed ubiquitously. Estrone-3-sulfate, Prostaglandin E2, benzyl penicillin Vasopressin and Thyroxin are transported by OATP3A1. OATP4A1 is expressed ubiquitously. Estrogens, thyroid hormones, Taurocholate, Unaprostone, benzyl penicillin, Prostaglandins can be transported by it. OATP4C1 is localized in the human proximal tubule cells at the basolateral membrane and hence it can mediate the uptake of its substrates from the blood in to the kidneys. Antidiabetic drug Sitagliptin, thyroid hormones, Methotrexate and Digoxin are transported by OATP4C1. OATP5A1 is considered to be the only one at the cDNA level and mRNA of SLCO6A1 was found to be detected in the testis. In the pharmacokinetics of several drugs, OATP transporters (especially, OATP1B1, 1A2, 1B3 and 2B1) play a significant role [53].

ABC drug transporters: ABC transporters play a significant role in the absorption, distribution and removal of drugs because of their expression in transporting epithelia including liver, intestine and kidney. ABC transporters that are involved in drug transport can be observed in the ABCB, ABCC and ABCG families. Treatment failure in cancer can be caused because majority of them were associated with Multi Drug Resistance (MDR) of tumor cells. The molecular weight ranges between 150-200 kDa and comprises of two transmembrane domains, each consisting of six transmembrane helices and two cytoplasmic ATP- binding domains [54]. To drive primary active drug efflux they bind and hydrolyze ATP which is directly linked to their ATPase activity.

By MDR1/ABCB1 gene, the MDR1/P-glycoprotein (P-gp) is encoded. Unusually, P-gp has broad substrate specificity, identifying hundreds of compounds ranging from small molecules of 350 Da up to polypeptides of 4000Da. A high number of P-gp substrates comes under the category of bulky, often polyvalent, organic cations that are classified a type II organic cations [55]. Crystal structures of mammalian P-gp were reported very recently, exhibiting distinct incomplete over lapping drug-binding sites in the internal cavity of the protein that provides the first molecular basis for its multispecificity [56]. P-gp expressed in various tissues is located on the apical side of intestine, kidney epithelia and liver where it decreases systemic drug exposure by limiting oral absorption and enhancing biliary and urinary excretion [57].

Nine full multi drug resistance protein (MRP) members have been found within the ABCC sub family. The most important drug transporters among them are MRP2/ ABCC2, MRP3 /ABCC3 and MRP4/ABCC4. The transport of organic anionic compounds can be mediated by MRPS in liver, intestine and kidneys [58]. MRPs are expressed with a barrier functions like placenta and brain capillaries. At the apical membrane of polarized cells, MRP2 is located emphasizing the significant function in the excretion of anionic drugs and conjugates. The cellular efflux of mainly glucuronidated drug conjugates from the liver and intestine in to the blood is mediated by MRP3 [59]. Dual membrane localization is a remarkable feature of MRP4 [60].

The transporter is localized at the basolateral membrane in hepatocytes, where as it is expressed at the apical membrane of renal proximal tubule cells. The sub cellular distribution of MRP4 has not been established in the intestine yet and in a colonic epithelial cell line, localization to both the basolateral and the apical membrane was found with a higher apical abundance [61,62].

Transporters for hepatic drug elimination

With high protein binding from the circulation, the liver has the capability to extract the drugs efficiently. Frequently, the hepatic uptake of drugs is followed by phase-I and phase-II biotransformation and efflux of the metabolites into bile and contributes to the hepatic first-pass effect. In drug elimination, it has been recognized that influx and efflux transporters expressed at the basolateral (sinusoidal) and apical (canalicular) membrane of hepatocytes acts as critical determinants. OATP1B1, OATP1B3, OATP2B1, OAT2 AND OCT1 are the drug influx transporters expressed at the sinusoidal membrane.

For majority of clinically relevant drugs like statin, macrolide antibiotics, sartam, glitazones and angiotensin converting enzyme, OATP1B1 is recognized to be most significant uptake transporter. For OATP1B1- mediated statin transport with Cyclosporine A, clinically relevant DDI have been described [63]. Similar substrate specificity has been observed for the homolog OATP1B3 and it is only expressed in the liver cells surrounding the central vein. In hepatobiliary elimination, the activity of these transporters is often the rate limiting step. In the interindividual variation in drug exposure and disposition, their inhibition and genetic variability are the critical factors. A strong association of SLCO1B1 variants with an increased risk of myopathy due to simvastatin was emphasized by a recent genome wide study. With high statin blood concentrations, these genotypes are known to be associated [64].

In the hepatic uptake of type I organic anions like indomethacin and salicylate, OAT2 could be involved and is expressed moderately [65]. The influx of type I organic cations into Liver cells is mediated by OCT1. It can also facilitate the efflux of cationic drugs back in to the blood as a bidirectional electrogenic uniporter depending on the electrochemical gradient. Among the most commonly prescribed drugs for the treatment of type-II diabetes, metformin is the most clinically important substrate and its antidiabetic action is dependent on uptake into liver cells [66-68]. In the vectorial transport of drugs and drug metabolites from blood into bile, efflux transporters expressed in the canalicular membrane represent the final step.

MATE 1 and MDR 1/P-gp mediates the excretion of type I and II cationic drugs respectively across the canalicular membrane. For MATE 1, Metformin is a good substrate and by active tubular secretion, the drug is mainly excreted into urine. For the canalicular efflux of conjugated and unconjugated anionic drugs, MRP2 and BCRP are primarily responsible. All phase II drug metabolites formed in the liver cells are

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006

not transformed to bile. At the sinusoidal membrane, the localization of MRP3 and MRP4 indicates that these conjugates are also transported back into the circulation and hence renal elimination can be done. Protein levels of both transporters are increased and have the ability to mediate the efflux of bile salts under cholestatic conditions as these are the substrates of both MRP3 and MRP4. Depending on the kinetic properties of the drug, MRP3 and MRP4 have a significant impact on the overall hepatic clearance. If uptake is the rate limiting step in elimination, their contribution will be negligible [69-71].

Transporters involved in tubular secretion of drugs

Transporters involved in tubular secretion of drugs include P-gp, OATP and OCT, their inhibition decreases the renal elimination, and leads to increased serum drug concentrations. Both probenecid and penicillin are transported through OATP. Probenecid competitively binds to OATP and gets excreted, thus it inhibits penicillin excretion and increase duration of action of penicillin. Probenecid produces similar effect on cephalosporins. So probenecid is combined with Penicillin or cephalosporin's to obtain a longer duration of action of these beta lactam antibiotics. Diuretics act from within the tubular lumen, and salicylates inhibit their secretion into tubular fluid, and reduce their effect. Verapamil and Quinidine reduce billary/renal excretion of Digoxin by inhibiting P-gp. Quinidine reduces tissue binding of Digoxin and also inhibits P-gp. Thus quinidine reduces biliary and renal clearance of Digoxin and increase susceptibility.

Alteration in urine flow or urine pH can produce interactions at the level of elimination. Diuretics increase the urine flow and tend to increase the urinary excretion of other drugs and their metabolites. When thiazide diuretics and Lithium are used concurrently, sodium depletion due to thiazide diuretics tends to reabsorb lithium from proximal tubule, and Lithium toxicity precipitates. Changing urine pH is a common method employed in management of drug overdose. Forced alkaline diuresis with the help of systemic alkaliser such as intravenous sodium bicarbonate is useful to manage overdoses with acidic substances such as barbiturates and salicylates. Sodium bicarbonate produces alkalinization and hence facilitates ionization of weak acids and inhibits their reabsorption. Hence elimination of weak acids is enhanced. As opposed to this, in condition of overdose with alkalies like Amphetamine and phencyclidine, acidification with ammonium chloride helps elimination by similar principle of ionization. It has been reported that salicylates, Furosemide and penicillin G may bind to active transporters and may interfere with certain drugs. Salicylates compete with OATP and reduce the tubular secretion of methotrexate, causing methotrexate toxicity.

Summary and Conclusions

DMEs and transporters are widely present in body and play an important role in the absorption, distribution, excretion and metabolism, efficacy, and toxicity of drugs. Investigation of metabolizing enzymes and transporters has developed rapidly since 1990s, the effects of many transporters on the pharmacokinetics of drugs and DDI have been reported. Methodological studies are very important for understanding the mechanism, considerations and evaluation of experiments and clinical studies on DMEs and transporters in DDIs. Overall, from a mechanistic perspective, transporters offer complexities that are distinct from those of DMEs. Typically, tissue-specific drug concentrations are determined by both uptake and efflux transporters within a tissue. Drug concentrations measured in plasma, therefore, may not reflect levels in organs such as liver and brain Furthermore, in contrast to DMEs, which are largely concentrated in the liver and intestine, transporters are present in varying abundance in all tissues in the body, and have important roles in drug distribution and tissue-specific drug targeting, as well as in drug absorption and elimination.

References

1. Kohler GI, Bode-Boger SM, Busse R, Hoopmann M, Welte T, et al. (2000) Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. Int J Clin Pharmacol Ther 38: 504-513. Link: https://goo.gl/yqAcis

2. Hohl CM, Dankoff J, Colacone A, Afilalo M (2001) Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med 38: 666-671. Link: https://goo.gl/HaQQTX

3. Leape LL, Bates DW, Cullen DJ, Cooper J, Demonaco HJ, et al. (1995) Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA 274: 35-43. Link: https://goo.gl/EdNHXz

4. Müller F, Fromm MF (2011) Transporter-mediated drug-drug interactions. Pharmacogenomics 12: 1017-1037. Link: https://goo.gl/KZxAqM

5. Pirmohamed M, Park BK (2003) Cytochrome P450 enzyme polymorphisms and adverse drug reactions. Toxicology 192: 23-32. Link: https://goo.gl/Sj42Y5

6. Teo YL, Ho HK, Chan A (2015) Metabolism-related pharmacokinetic drug-drug interactions with tyrosine kinase inhibitors: current understanding, challenges and recommendations. Br J Clin Pharmacol 79: 241-253. Link: https://goo.gl/1E79Qs

7. Adams DH, Ju C, Ramaiah SK, Uetrecht J, Jaeschke H (2010) Mechanisms of immune-mediated liver injury. Toxicol Sci 115: 307-321. Link: https://goo.gl/u2DzKv

8. Yu J, Ritchie TK, Mulgaonkar A, Ragueneau-Majlessi I (2014) Drug disposition and drug-drug interaction data in 2013 FDA new drug applications: a systematic review. Drug Metab Dispos 42: 1991-2001. Link: https://goo.gl/ot1gA2

9. Obach RS, Walsky RL, Venkatakrishnan K, Houston JB, Tremaine LM (2005) In vitro cytochrome P450 inhibition data and the prediction of drug-drug interactions: qualitative relationships, quantitative predictions, and the rank-order approach. Clin Pharmacol Ther 78: 582-592. Link: https://goo.gl/G3J9G2

10. Zhang L, Zhang YD, Zhao P, Huang SM (2009) Predicting drug-drug interactions: an FDA perspective. AAPS J 11: 300-306. Link: https://goo.gl/RfEMY2

11. Greenblatt DJ (2014) In vitro prediction of clinical drug interactions with CYP3A substrates: we are not there yet. Clin Pharmacol Ther 95: 133-135. Link: https://goo.gl/nr88Fm

12. Guengerich FP (1995) Cytochrome P450: Structure, Mechanism, and Biochemistry, 2nd edition, Chapter 14. Edited by Paul R. Ortiz de Montellano, Plenum Press, New York. Link: https://goo.gl/kLwseH

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006

13. Parkinson A (1996) Toxicology: The Basic Science of Poisons, 5th edition, Chapter 6. Edited by Curtis D. Klassen, McGraw-Hill. Link: https://goo.gl/JTkVbG

14. Nelson DR (1999) Cytochrome P450 and the individuality of species. Arch. Biochem Biophys 369: 1-10. Link: https://goo.gl/fNmUbX

15. Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP (1994) Inter individual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther 270: 414-423. Link: https://goo.gl/DJgk7o

16. Ortiz de Montellano PR (1995) Cytochrome P450: Structure, Mechanism, and Biochemistry, 2nd Edition, Chapter 8, edited by Paul R. Ortiz de Montellano, Plenum Press, New York. Link: https://goo.gl/vQxCwX

17. Yamazaki H, Johnson WW, Ueng YF, Shimada T, Guengerich FP (1996) Lack of electron transfer from cytochrome b5 in stimulation of catalytic activities of cytochrome P450 3A4. Characterization of a reconstituted cytochrome P450 3A4/NADPH-cytochrome P450 reductase system and studies with apo-cytochrome b5. J Biol Chem 271: 27438-27444. Link: https://goo.gl/9KrZK2

18. Rettie AE, and Fisher MB. (1999) Handbook of Drug Metabolism, pp131-147, edited by Thomas F. Woolf, Marcel Dekker, Inc, New York.

19. Ziegler DM (1993) Annu Rev Pharmacol Toxicol 33: 179. Link: https://goo.gl/8Qu1w5

20. Birgit L Coffman, Gladys R Rios, Christopher D King, Thomas R Tephly (1997) Human UGT2B7 Catalyzes Morphine Glucuronidation Drug Metab Dispos. 25: 1-4. Link: https://goo.gl/aSqEqp

21. Jennifer J, Bouska, Randy L, Bell, Carole L, et al. (1997) Improving the In Vivo Duration of 5-Lipoxygenase Inhibitors. Drug Metab Dispos 25:1032-1038. Link: https://goo.gl/fFpQ1P

22. Radominska-Pandya A, Piotr JC, Joanna M L, Eric B,Peter IM (1999) Structural and functional studies of UDP-glucuronosyl transferases. Drug Metab Rev 31: 817-899. Link: https://goo.gl/RS2Yfd

23. McCall J, James W Aiken, Constance G Chidester, Donald W DuCharme, et al. (1983) Pyrimidine and triazine 3-oxide sulfates: a new family of vasodilators. J Med Chem 26: 1791-1793. Link: https://goo.gl/gTmmbq

24. Ronald D Sekura, Carol J Marcus, Ellen Sue Lyon, William B Jakoby (1979) Assay of sulfotransferases. Analytical Biochemistry 95:82-86. Link: https://goo.gl/9xGrtu

25. Weinshilboum RM, D M Otterness, I A Aksoy, T C Wood, R B Raftogianis, et al. (1997) FASEB J 11: 3-14. Link: https://goo.gl/5ViXdT

26. Raftogianis RB, Thomas C.Wood, Diane M O, Jon AVL, Richard MW (1997) BBRC 239: 298-304. Link: https://goo.gl/NvkLNT

27. Weber W (1997) Pharmacogenetics, Oxford University Press, New York.

28. Degtyarenko KN (1995) Structural domains of P450-containing monooxygenase systems. Protein Engineering 8: 737-747. Link: https://goo.gl/TNsV1E

29. Vercruysse A (1997) Toxicologie. Cursus 2de graad apotheker VUB ;pp.17.

30. Buck ML (1997) The cytochrome P450 enzyme system and its effect on drug metabolism. Pediatric Pharmacotherapy 3

31. Meyer JM, Rodvold KA (1996) Drug biotransformation by the cytochrome P-450 enzyme system. Infect Med 13: 463-464. Link: https://goo.gl/dxWCD6

32. Kolars JC, Lown KS, Schmielin-Ren P, Ghosh M, Fang C (1994) CYP3A4 gene expression in gut epithelium. Pharmacogenetics.4:247-59. Link: https://goo.gl/SpmBhc

33. Wrighton SA, Ring BJ, Watkins PB, Vandenbranden M (1989) Identification of a polymorphically expressed member of the human cytochrome P-450 III family. Mol Pharmacol. 36: 97-105. Link: https://goo.gl/p3jKFp

34. Dossing M, Pilsgaard H, Rasmussen B, Poulsen HE (1983) Time course of phenobarbital and cimetidine mediated changes in hepatic drug metabolism. Eur J Clin Pharmacol 25: 215-22. Link: https://goo.gl/sKBnKA

35. Villeneuve JP, Pichette V (2004) Cytochrome P450 and liver diseases. Curr Drug Metab 5: 273-282. Link: https://goo.gl/qMVxW5

36. Verbeeck RK (2008) Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 64: 1147-1161. Link: https://goo.gl/hDRxW4

37. Farrell G (1999) Effects of disease on expression and regulation of CYPs. Mol Aspects Med 20: 55-70. Link: https://goo.gl/ZWf5to

38. Huet PM, Villeneuve JP (1983) Determinants of drug disposition in patients with cirrhosis. Hepatology 3: 913-918. Link: https://goo.gl/PCfcr2

39. Hung DY, Chang P, Cheung K, McWhinney B, Masci PP, et al. (2002) Cationic drug pharmacokinetics in diseased livers determined by fibrosis index, hepatic protein content, microsomal activity, and nature of drug. J Pharmacol Exp Ther 301: 1079-1087. Link: https://goo.gl/jshN7p

40. Sandson NB, Marcucci C, Bourke DL, Smith-Lamacchia R (2006) An interaction between aspirin and valproate: the relevance of plasma protein displacement drug-drug interactions. Am J Psychiatry 163: 1891-1896. Link: https://goo.gl/bhJMXj

41. Pietro Palatini, Sara De Martin (2016) Pharmacokinetic drug interactions in liver disease: An update. World J Gastroenterol 22: 1260-1278. Link: https://goo.gl/b5K16L

42. Tímea Borbás, Bernadett Benk, Imola Szabó, Balázs Dalmadi, Károly Tihanyi (2006) Insulin in flavin-monooxygenase regulation. Flavin-containin monooxygenase and cytochrome P450 activities in experimental diabetes. European Journal of Pharmaceutical Sciences, 28: 1-2 Link: https://goo.gl/6nxzdc

43. Miroslav Dostalek, Michael H Court , Bingfang Yan, Fatemeh Akhlaghi (2011) Significantly reduced cytochrome P450 3A4 expression and activity in liver from humans with diabetes mellitus. British Journal of Pharmacology 163: 937-947. Link: https://goo.gl/hSk941

44. Fredriksson R, Nordstrom KJ, Stephansson O, Hagglund MG, Schioth HB (2008) The solute carrier (SLC) complement of the human genome: phylogenetic classification reveals four major families. FEBS Lett 582: 3811-3816. Link: https://goo.gl/T7vWna

45. Dean M, Allikmets R (2001) Complete characterization of the human ABC gene family. J Bioenerg Biomembr 33: 475 479. Link: https://goo.gl/cp8SBu

46. Sheps JA, Ling V (2007) Preface: the concept and consequences of multidrug resistance. Pflugers Arch 453: 545-553. Link: https://goo.gl/nPiaF5

47. Szakacs G, Varadi A, Ozvegy-Laczka C and Sarkadi B (2008) The role of ABC transporters in drug absorption, distribution, metabolism, excretion and toxicity (ADME-Tox). Drug Discov Today 13:379-393. Link: https://goo.gl/Ti9FLj

48. Dobson PD, Kell DB (2008) Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule? Nat Rev Drug Discov 7: 205-220. Link: https://goo.gl/AfFg5e

49. Shitara Y, Sato H, Sugiyama Y (2005) Evaluation of drug-drug interaction in the hepatobiliary and renal transport of drugs. Annu Rev Pharmacol Toxicol 45: 689-723. Link: https://goo.gl/4URMp9

50. Zair ZM, Eloranta JJ, Stieger B, Kullak-Ublick GA (2008) Pharmacogenetics of OATP (SLC21/SLCO), OAT and OCT (SLC22) and PEPT (SLC15) transporters in the intestine, liver and kidney. Pharmacogenomics 9: 597-624. Link: https://goo.gl/Zqtd6G

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006

51. Tozer TN, Rowland M (2006) Introduction to Pharmacokinetics and Pharmacodynamics. Lippincott Williams & Wilkins: Philadelphia. Link: https://goo.gl/hR3iy8

52. Ho RH, Kim RB (2005) Transporters and drug therapy: implications for drug disposition and disease. Clin Pharmacol Ther 78: 260-277. Link: https://goo.gl/KNV4Qy

53. A Kalliokoski, Niemi M (2009) Impact of OATP transporters on pharmacokinetics. British Journal of Pharmacology 158: 693-705. Link: https://goo.gl/dmY4AM

54. Locher KP (2009) Review. Structure and mechanism of ATP-binding cassette transporters. Philos Trans R Soc Lond B Biol Sci 364: 239-245. Link: https://goo.gl/wNczYw

55. Zhou SF (2008) Structure, function and regulation of P-glycoprotein and its clinical relevance in drug disposition. Xenobiotica 38: 802-832. Link: https://goo.gl/BK7jrn

56. Aller SG, Yu J,Ward A,Weng Y, Chittaboina S, Zhuo R, et al. (2009) Structure of P-glycoprotein reveals a molecular basis for poly-specific drug binding. Science 323: 1718-1722. Link: https://goo.gl/mTqwEi

57. Stieger B, Meier Y, Meier PJ (2007) The bile salt export pump. Pflugers Arch 453: 611-620. Link: https://goo.gl/e6oyiT

58. Deeley RG, Westlake C, Cole SP (2006) Transmembrane transport of endo- and xenobiotics by mammalian ATP-binding cassette multidrug resistance proteins. Physiol Rev 86: 849-899. Link: https://goo.gl/bXLVzv

59. Borst P, de Wolf C, van de Wetering K (2007) Multidrug resistance-associated proteins 3, 4, and 5. Pflugers Arch 453:661-673. Link: https://goo.gl/D8dFpd

60. Van Aubel RA, Smeets PH, Peters JG, Bindels RJ, Russel FG (2002) The MRP4/ABCC4 gene encodes a novel apical organic anion transporter in human kidney proximal tubules: putative efflux pump for urinary cAMP and cGMP. J Am Soc Nephrol 13: 595-603. Link: https://goo.gl/pKvWnv

61. Li C, Krishnamurthy PC, Penmatsa H, Marrs KL, Wang XQ, et al. (2007) Spatiotemporal coupling of cAMP transporter to CFTR chloride channel function in the gut epithelia. Cell 131: 940-951. Link: https://goo.gl/gNCntH

62. Russel FG, Koenderink JB, Masereeuw R (2008) Multidrug resistance protein 4 (MRP4/ABCC4): a versatile efflux transporter for drugs and signalling molecules. Trends Pharmacol Sci 29: 200-207. Link: https://goo.gl/u9yvB3

63. Endres CJ, Hsiao P, Chung FS, Unadkat JD (2006) The role of transporters in drug interactions. Eur J Pharm Sci 27:501-517. Link: https://goo.gl/1YzmYV

64. Link E, Parish S, Armitage J, Bowman L, Heath S, et al. (2008) SLCO1B1 variants and statin-induced myopathy - a genomewide study. N Engl J Med 359: 789-799. Link: https://goo.gl/KHWpnS

65. Rizwan AN, Burckhardt G (2007) Organic anion transporters of the SLC22 family: biopharmaceutical, physiological, and pathological roles. Pharm Res 24: 450-470. Link: https://goo.gl/VeLZe5

66. Shikata E, Yamamoto R, Takane H, Shigemasa C, Ikeda T, et al. (2007) Human organic cation transporter (OCT1 and OCT2) gene polymorphisms and therapeutic effects of metformin. J Hum Genet 52: 117-122. Link: https://goo.gl/fvfJtt

67. Shu Y, Sheardown SA, Brown C, Owen RP, Zhang S, et al. (2007) Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. J Clin Invest 117: 1422-1431. Link: https://goo.gl/mr13DA

68. Kaixin Zhou, Louise A Donnelly, Charlotte H Kimber, Peter T Donnan, Alex SF Doney, Graham Leese, Andrew THattersley, et al. (2009) Reduced-Function SLC22A1 Polymorphisms Encoding Organic Cation Transporter 1 and Glycemic Response to Metformin: A GoDARTS Study. Diabetes 58: 1434-1439. Link: https://goo.gl/AVBFti

69. Nies AT, Keppler D (2007) The apical conjugate efflux pump ABCC2 (MRP2). Pflugers Arch 453: 643-659. Link: https://goo.gl/sdWikx

70. Kusuhara H, Sugiyama Y (2009) In vitro-in vivo extrapolation of transporter-mediated clearance in the liver and kidney. Drug Metab Pharmacokinet 24: 37-52. Link: https://goo.gl/GKQ7qK

71. Nies AT, Schwab M, Keppler D (2008) Interplay of conjugating enzymes with OATP uptake transporters and ABCC/MRP efflux pumps in the elimination of drugs. Expert Opin Drug Metab Toxicol 4: 545-568. Link: https://goo.gl/wWkdE2

Citation: Srinivas M, Thirumaleswara G, Pratima S (2017) Cytochrome p450 Enzymes, Drug Transporters and their role in Pharmacokinetic Drug-Drug interactions of Xenobiotics: A Comprehensive Review. Peertechz J Med Chem Res 3(1): 001-011. DOI: http://dx.doi.org/10.17352/ojc.000006