Pharmacokinetics and Metabolic Drug Interactions

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Abstract: Pharmacokinetics and drug metabolism play an important role as determinants of *in vivo* drug action. The CYP450 enzyme family plays a determinant role in the biotransformation of a vast number of structurally diverse drugs. Many drug interactions are a result of the inhibition or induction of CYP enzymes. The non-compartmental pharmacokinetic analysis is the most used method for analyzing data from a drug interaction study. Compartmental analysis can be also useful and sometimes more informative than non-compartmental analysis. Many efforts to reduce polypharmacy are important, and pharmacokinetic tools used to study the mechanism of drug-drug interactions may help in a better management of pharmacotherapy including the avoidance of clinically relevant drug interactions.

Keywords: Pharmacokinetics, Metabolism, Drug interactions.

1. INTRODUCTION

The development of novel therapeutical agents should provide a delicate balance between the chemistry, pharmacology and pharmacokinetics of the drug. Due to ethical constraints, relevant pharmacokinetic and metabolism studies must be carried out extensively in laboratory animals or *in vitro* systems before first drug administration in humans. The complete safety profile of a new drug will be defined only after it has been approved and is in use on the market. In clinical practice, it is not possible to prevent co-prescription of different drugs, with clinical significant interactions.

The biological response of the human body to an exogenous compound e.g. a drug, is dependent on a complex network of factors, as illustrated in Fig. (**1**) [1].

Drug-drug interactions occur when one therapeutic agent either alters the concentration (pharmacokinetic interactions) or the biological effect of another agent (pharmacodynamic interactions). Pharmacokinetic drug-drug interactions can occur at the level of absorption, distribution, or clearance of the affected agent. Many drugs are eliminated by metabolism. The microsomal reactions that have been studied the most involve cytochrome P (CYP) 450 family of enzymes, of which a few are responsible for the majority of metabolic reactions involving drugs. These include the isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 [2].

Enzyme inhibition refers to the decrease in metabolic enzyme activity due to the presence of an inhibitor. Drug metabolism by CYP450 can be inhibited by any of the following three mechanisms: competitive inhibition, noncompetitive inhibition and uncompetitive inhibition. Inhibition of enzyme activity may result in higher concentrations and/or prolonged half-life of the substrate drug, which enhances the potential for toxic side effects. The clinical significance of a specific drug-drug interaction depends on the degree of accumulation of the substrate and the therapeutic window of the substrate [3].

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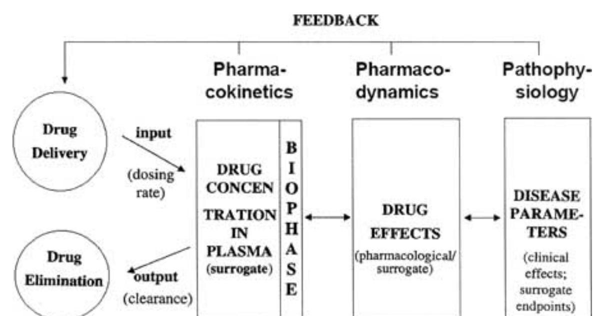

Fig. (1). Schematic illustration of the complex interrelationships of factors that influence drug response [1].

Enzyme induction is associated with an increase in enzyme activity. For drugs that are substrates of the isoenzyme induced, the effect is to lower the concentration of these substrates. The clinical consequence of the presence of an inducing agent and the resultant decrease in concentration of the substrate may mean a loss of efficacy.

Several of the drug metabolizing enzymes are polymorphic, having more than one variant of the gene. Although the CYP isozymes generally have similar functional properties, each one is different and has a distinct role. This polymorphism forms a basis for interindividual differences in the efficacy of drug treatment, side effects of drugs and the toxic and carcinogenic action of xenobiotics. The variability associated with the CYP450 enzymes in each individual result in a marked difference in response when the same drug and the dose are administered to different individuals. Genetic polymorphism of CYP450 enzymes characterizes the general population into three groups: extensive metabolizers, poor metabolizers and ultra extensive metabolizers [4].

The quantitative study of the time course of drug absorption, distribution, metabolism and excretion (ADME) allows the calculation of several important pharmacokinetic parameters such as area under the curve (AUC), bioavailability, clearance and apparent volume of distribution. Pharmacokinetic data analysis using mathematical models is known as compartmental pharmacokinetics. The rate transfer

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between compartments and the rate of elimination are assumed to be following first-order kinetics. However, non-compartmental analysis can be used to determine pharmacokinetic parameters without fitting the pharmacokinetic data to any specific compartmental model, assuming the data follow linear pharmacokinetics. Non-compartmental methods are based on the theory of statistical moments and parameters as the mean residence time, apparent volume of distribution, etc. The basic equations cannot be applied to all drugs. In some situations, complex mathematical models are required to express the pharmacokinetic profiles [5].

In addition to the above aspects of the pharmacokinetics of the parent compound, the pharmacokinetics of a metabolite is also characterized by its formation. The most common sites of biotransformation of the parent drug into metabolite occur in liver, gut, plasma, kidneys and lungs. If the metabolite is formed pre-systemically in the gut, the pharmacokinetics of the metabolite is not only governed by its rate of formation but also by its rate of absorption into the systemic circulation. Many drugs that undergo extensive first-pass metabolism in the gut are generally metabolized by phase I enzymes (specifically CYP450 enzymes) [6].

When a drug-drug interaction occurs, the pharmacokinetics of the inhibited or induced drug is altered. In some instances, there may be dual interactions where both drugs may be inhibited or induced. When the drug is biotransformed into one or more active metabolites, they are also responsible for the pharmacodynamics and therapeutic effect. A differentiation between gut and hepatic metabolism is also of importance in bioequivalence assessment. Pharmacokinetic and pharmacodynamic methods are powerful tools to describe and understand drug action in the intact organism. Integration of the methods can be used to verify that plasma pharmacokinetics is a suitable surrogate for tissue pharmacodynamics [7].

All the above reasons and much more, suggest that the pharmacokinetics is a useful method to study the influence of drug-drug interaction on the values of the pharmacokinetic parameters, which in turn will modify the drug plasma levels with the risk of clinically significant consequences. On the other hand, pharmacokinetic analysis can elucidate the mechanisms of drug-drug interactions, which will clarify important aspects of human pharmacology.

2. DRUG METABOLISM

2.1. Types of Drug Metabolism

Drug metabolism, also known as drug biotransformation, has the objective of making xenobiotics more hydrophilic so they can be efficiently eliminated by the kidney. To increase hydrophilicity, a polar group is added or unmasked. Often the metabolite is inactive and the chemical change alters the shape and charge of the drug so it can no longer bind to its receptor and/or exerts its effect on the receptor's function. In some cases the metabolite retains its pharmacologic effects, it is an active metabolite. In other cases, the parent drug is pharmacologically inactive and requires metabolism for a pharmacologic effect; this type of drug is a prodrug.

There are two major categories of metabolism reactions called Phase I and Phase II [8, 9]. Phase I reactions refers to a set of reactions that result in relatively small chemical changes that make compounds more hydrophilic and also provide a functional group that is used to complete Phase II reactions. Phase I reactions are concerned with addition or unmasking of functional, polar moiety, the chemical processes being the oxidation and/or reduction, or hydrolysis. Phase I metabolism can occur during drug absorption, either in the gut wall or in the liver, before the drug reaches the systemic circulation [5]. The presystemic clearance, or first-pass metabolism, determines the fraction of the oral dose that will reach the systemic circulation, i.e. the fraction of the drug that is bioavailable.

The majority of Phase I reactions are mediated by a large family of cytochrome P450 enzymes. Functionalization reactions of Phase I are reactions which generate functional group as in hydroxylation, or "unmask" functional group as in ester hydrolysis.

Oxidations carried out by P450's can be: aromatic oxidations (propranolol, phenobarbital, phenytoin, phenylbutazone, amphetamine, warfarin); aliphatic oxidations (amobarbital, secobarbital, chlorpropamide, ibuprofen, meprobamate, glutethimide, phenylbutazone, digitoxin); epoxidations (carbamazepine); N-dealkylations (morphine, caffeine, theophylline); O-dealkylations (codeine); S-dealkylations (6-methylthiopurine); N-oxidations, primary amines (chlorphentermine), secondary amines (acetaminophen), tertiary amines (nicotine, methaqualone); S-oxidations (thioridazine, cimetidine, chlorpromazine); deaminations (amphetamine, diazepam).

There are also non-P450 oxidations: monoamine oxidase reactions, different mechanism with the same result as P450 deamination (formation of imine followed by hydrolysis); flavin monooxygenase reactions (FMO) (but P450 reductases also use flavin as FAD, flavin adenine dinucleotide, and FMN, flavin mononucleotide) [8, 9, 10].

Other phase I reactions: reductions, e.g. nitro reduction (chloramphenicol, clonazepam), and azo group reduction (prontosil, tartrazine); hydrolysis: derivatives of carboxylic acid hydrolysis: esters (cocaine, procaine, tetracaine, benzocaine; succinylcholine), amides (lidocaine, mepivacaine, bupivacaine, etidocaine, prilocaine). Glucuronide hydrolysis gives rise to enterohepatic recirculation, significantly prolonging the life of some drugs, because their sufficiently lipophilic metabolites are reabsorbed into the portal circulation from which they can reenter the liver [8, 9, 10].

Compounds that remain in the circulation after undergoing Phase I metabolism often undergo Phase II metabolism. Phase II reactions are characterized by conjugation with small, endogenous substance, often taking advantage of functional group added in Phase I. The transferases that mediate Phase II reactions are important not only for eliminating drugs but also for detoxifying reactive drug metabolites, which are mostly produced by prior metabolism by cytochrome P450 enzymes. In some cases in which the parent drug has an appropriate site, Phase II metabolism may occur first [8, 9, 10].

Glucuronide formation is an important step in the elimination of many important endogenous substances from the body, including bilirubin, bile acids, steroid hormones,

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and biogenic amines as serotonin. Many of these compounds are also substrates for sulfonyltransferases. The most common reaction occurs by transfer of a glucuronic acid moiety from uridine-diphosphate glucuronic acid (UDPGA) to an acceptor molecule. This process is termed either glucuronosylation or glucuronidation [11]. When enzymes catalyze this reaction, they are also referred to as UDP-glucuronosyltransferases (UGTs) (acetaminophen, ibuprofen, morphine, diazepam, meprobamate, digitoxin, digoxin).

Other Phase II reactions: sulfation (acetaminophen, methyldopa, 3-hydroxycoumarin, estrone); glutathione conjugation (ethacrinic acid); acetylation (sulfonamides, isoniazid, clonazepam, dapsone); methylation (dopamine, epinephrine, histamine, thiouracil) [8, 9, 10].

2.2. Cytochrome P450 System

The cytochrome P450 (CYP) family of heme monooxygenases comprises the most important group of phase 1 enzymes [12, 13]. These enzymes are characterized by a maximum absorption wavelength of 450 nm in their reduced state in the presence of carbon monoxide.

The term cytochrome P-450 refers to a group of enzymes which are located on the endoplasmic reticulum. The metabolic enzymes are also present in high concentrations in the enterocytes of the small intestines with small quantities in extrahepatic tissues (kidneys, lungs, brain etc). The nomenclature employs a three – tier classification consisting of the family (> 36% homology in amino acid sequence), subfamily (70% homology), and individual gene (ex. CYP3A4). Naming a cytochrome P450 gene includes root symbol "CYP" for humans ("Cyp" for mouse and Drosophila), an Arabic numeral denoting the CYP family (e.g. CYP2), letters A,B,C indicating subfamily (e.g. CYP3A) and another Arabic numeral representing the individual gene/isoenzyme/isozyme/isoform (e.g. CYP3A4) [12]. Each isoenzyme of CYP is a specific gene product with characteristic substrate specificity. These enzymes oxidate a wide range of both endogenous and exogenous compounds using atmospheric oxygen (O_2) [13].

The cytochrome P450 gene family contains 60 to 100 different genes, of which only a small group is involved in drug and chemical transformations. In the human liver there are at least 12 distinct CYP enzymes. At present it appears that from about 30 isozymes, only six isoenzymes from the families CYP1, 2 and 3 are involved in the hepatic metabolism of the most drugs. The most important P450 isoenzyme is CYP3A4 (50% of the P450 metabolism) followed by CYP2D6 (20%), CYP2C9 and CYP2C19 (together 15%). The remaining is carried out by CYP2E1, CYP2A6 and CYP1A2. The genes for CYP2D6, CYP2C9, CYP2C19 and CYP2A6 are functionally polymorphic. Therefore approximately 40% of human P450 dependent drug metabolism is carried out by polymorphic enzymes (for a list of all currently known cytochrome P450 gene alleles refer to http: //www.imm.ki.se/ CYPalleles/).

2.3. Genetic Polymorphisms in Drug Metabolism and Disposition

Genetic polymorphism with clinical implications has been described for 2D6, 2C19, 2C9, 1A2, 3A4 [e.g. 14, 15, 16].

The human genome contains three billions base pairs of nucleotides in the haploid genome of which about only 3% are genes [17]. A gene is the basic unit of heredity that contains the information for making one RNA and in most cases, one polypeptide. The number of genes in humans is estimated at 40.000 to 100.000. Polymorphism is defined as the existence of two or more genetically determined forms (alleles) in a population in substantial frequency. A polymorphic gene is one at which the frequency of the most common allele is less than 0.99. It has been estimated that in each human individual 20% of the proteins and hence the genes exist in a form that is different from the majority of the population. In a sample of 71 human genes it was observed that 28% were polymorphic and that the average heterozygosity was 0.067. Heterozygosity is defined as the proportion in a population of diploid genotypes in which the two alleles for a given gene are different [18].

Polymorphism in drug metabolizing enzymes is caused by mutations in genes that code for specific biotransformation enzyme [17]. Generally they follow the autosomal recessive trait that means that the mutations are not sex linked (autosomal) and that one mutated allele does not express the phenotype when combined with a normal, not mutated (dominant) allele [19].

Genes can be mutated in several ways: a nucleotide can be changed by substitution, insertion or deletion of a base. If changes refer to one or few bases, these mutations are called point mutations. Larger changes can exist also, deletion of the entire gene or duplication of the entire gene. Some point mutations are silent mutations: they have no consequences at the point level. Other point mutations will affect amino acid sequence and will affect the biological function of the protein [20].

For drug metabolizing enzymes, the molecular mechanisms of inactivation include splice site mutations resulting in exon skipping (CYP2C19), micro satellite nucleotide repeats (CYP2D6), gene duplication (CYP2D6), point mutations in early stop codons (CYP2D6), enhanced proteolysis (TPMT), altered pro-moter functions (CYP2A5), critical amino acid substitutions (CYP2C19), or large gene deletions (CYP2D6). Conversely, gene duplication can be associated with enhanced activity of some drug metabolizing enzymes (CYP2D6). For many genes encoding drug metabolizing enzymes the frequency of single nucleotide polymorphisms (SNPs) and other genetic defects appears to be more than the 1 per 1000 nucleotide. It may be that genetic polymorphisms of drug metabolizing enzymes are quite common because these enzymes are not essential from evolutionary perspective. However some essential receptors have more mutations than would be predicted from the 1 in 1000 rate.

In the case of CYP2D6 gene some polymorphic modifications are known [20, 21].

Individuals with normal metabolic enzyme activities are often called extensive metabolizers (EM). Ultra-rapid metabolism (CYP2D6*2xN) is caused by multiple functional CYP2D6 genes, causing an increased amount of CYP2D6 to be expressed. Gene duplication or sometimes multiplication

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leads to the ultra-rapid (UR) phenotype. A homozygous combination of non-coding alleles leads to the poor metabolizer (PM) phenotype, whereas heterozygous wild type or combinations of alleles with diminished enzyme activity lead to reduced CYP2D6 activity. The prevalence of CYP2D6 PM phenotype differs per race and is reported to be 5 to 10 % in white populations and 1 to 2% in Orientals [22].

The 2D6 isoenzyme represents <5% of total CYP proteins, but is the most intensively studied because of its large number of substrates (30-50 drugs) and its genetic polymorphism [24, 25, 61, 62]. Some of the cardiovascular agents and psychoactive drugs are metabolized *via* CYP2D6. Therefore, the clinical impact of impaired metabolism is thought to be the greatest in these classes of drugs. Some CYP2D6 substrates are: encainide, flecainide, mexiletine, propafenone; metoprolol, propranolol, timolol, amitriptylline, clomipramine, desipramine, imipramine, nortriptylline, fluoxetine, fluvoxamine, maprotiline, mianserine, paroxetine, trazodone, etc [23, 24, 25].

The 2C subfamily consists of isoenzymes 2C9, 2C10, 2C19 and others. CYP2C9 has a polymorphic distribution in the population and is missing in 1% of Caucasians. The isoenzyme CYP2C19 also exhibits genetic polymorphism. Its genetic absence in such a high percentage of Asians (20-30%) is notable.

In the case of CYP2C19 gene, two null-alleles, *2 and *3, have been described to account for approximately 87% of all PM in Caucasians and 100% of all PMs in Orientals [25, 26]. Three non-coding alleles (19*4, 19*5 and 19*6) have been described but the frequencies of these alleles are expected to be below 1% in Caucasians. Deficiency of CYP2C19 occurs with a prevalence of PMs of 2-5% among Europeans, 4-5% Black Africans, 6% Black Americans and 12-23% among Orientals [20]. Well known substrates of CYP2C19 are drugs like the sedative drug diazepam, and the proton pump inhibitor omeprazole, or lansoprazole.

The variability of CYP3A4 activity is quite severe. The intrinsic clearance for CYP3A4 metabolized substances can vary among individuals, with interindividual differences of factors of 10 or higher [28].

CYP3A4 is an isoenzyme involved in Phase I oxidative metabolism of many substances. It is the most important hepatic CYP-enzyme accounting for approximately 25% of all liver CYP450s [27]. Since CYP3A4 is also present in the small intestine, it has a significant effect on the first-pass metabolism of CYP3A4 substrates. A number of drugs metabolized chiefly by CYP3A4: fentanyl; carbamazepine; azitromycin, clarithromycin, erythromycin; fluconazole, ketoconazole, miconazole; indinavir, ritonavir, saquinavir; tamoxifen; amiodarone, lidocaine, quinidine; amlodipine, diltiazem, felodipine, nifedipine, nimodipine, nitrendipine, verapamil; fluvastatin, pravastatin; loratadine, terfenadine; cisapride; cyclosporine, tacrolimus; sertraline; alprazolam, midazolam, triazolam, zolpidem; dexamethasone, prednisone, testosterone, etc [23,24,25]. Although CYP3A is not polymorphic in its distribution, its activity varies over 50-fold in the general population [72].While polymorphisms in CYP3A4 are not recognized, CYP3A5 has known ethnic differences in its expression and there is ongoing interest in whether these differences manifest themselves in altered pharmacokinetics and clinical consequences of therapy with substrates for CYP3A [79].

CYP1A2 is an important drug metabolizing enzyme in the liver that metabolizes many commonly used drugs and this is the only isoenzyme affected by tobacco. Cigarette smoking may lead to a three-fold increase in 1A2 activity. Their clearances are all increased by smoking. Thus the people who smoke may require higher doses of some of the medications that are substrates of CYP1A2 [24, 25, 61, 62].

The individual status of the activity of drug metabolizing enzymes which in its turn is a method of phenotyping, can be assessed using enzyme specific probe drugs [28,29]. The drug is administered to a patient and the excretion rate (metabolic rate) is measured after several hours. Simultaneous assessment of *in vivo* activities of more than one enzyme may be performed by a multi-enzyme probe approach or by the cocktail approach [30]. For CYP2D6 dextrometorphan, sparteine, debrisoquine and metoprolol have been described as probe drugs [29]. *In vivo* enzyme activity of CYPsC19 gene can be assessed by measurement of the metabolic ratio of an enzyme specific probe, as mephenitoin, omeprazole and proguanil [30].Examples of multi-drug cocktails to assess P450 activity are: dextromethorphan, mephenytoin, or sparteine, mephenytoin, or debrisoquine, mephenytoin, or dextromethorphan, proguanil, for CYP2D6 and CYP2C19; dextromethorphan, caffeine for CYP2D6, NAT2, XO,CYP1A2; “Pittsburgh cocktail” caffeine, chlorzoxazone, dapsone, debrisoquine, mephenytoin, for NAT2, CYP1A2, CYP2E1, CYP3A4, CYP2D6 and CYP2C19 [26,31].

Genotyping is another tool to describe populations. Detection of mutations in genomic DNA is difficult to realize because one single point mutation has to be determined in the midst of three billion base pairs. The classical method is restriction fragment length polymorphism (RFLP) followed by Southern blotting. The polymerase chain reaction (PCR) has revolutionized the analysis of genetic diseases and polymorphisms, being the basis for almost all methods for the detection of single nucleotide polymorphisms (SNPs).

There are three ways to get information on metabolizing enzyme activities: study the genes that code for the enzyme; study the level of enzyme expression in a certain tissue, and assess actual enzyme activity using an enzyme specific probe. Genotyping is a more simple procedure compared to phenotyping. But in population studies, phenotyping might be helpful in detecting interethnic differences, or in studies to detect enzyme induction or inhibition [32].

Such polymorphisms may or may not have clear clinical significance for affected medications, depending on the importance of the enzyme for the overall metabolism of a medication, the expression of the other drug metabolizing enzymes in the patient, the therapeutic index of the drug, the presence of concurrent medications or illnesses, and other polygenic factors that impact drug response.These common polymorphisms in drug receptors and drug metabolizing enzymes are often major determinants of interindividual differences in drug response. The adverse drug reactions

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could be related to genetically determined variation of drug-metabolizing enzymes in the liver [18, 33, 34, 35].

2.4. Ontogeny of Metabolic Enzymes

Earlier studies considered the presence of CYP enzymes in the embryo and fetus to be a kind of adaptive response toward exposure to environmental challenges. Other studies have suggested a number of forms of CYP450 may be present constitutively in the conceptus [36]. The developmental pharmacology has an important impact on the drug disposition, action and therapy in infants and children [37].

Pharmacokinetics and Pharmacodynamics are very different in children and adults [37].The pharmacokinetics of many drugs vary with age [37].Infants and children are very different from adults in terms of societal, psychosocial, behavioral and medical perspectives. Developmental changes affect profoundly the responses to medications and produce a need for age-dependent adjustments in doses. The levels of most phase I and phase II enzymes rise during the first weeks after the birth, regardless of gestational age at birth. The capacity of the human liver to eliminate xenobiotic compounds during the neonatal period is effective and the intensity of biotransformation depends primarily on the level of maturation of phase I enzymes. This makes it hazardous to extrapolate data for adults to children.

The use of pharmacokinetic data to examine the ontogeny of a drug metabolizing enzyme is well illustrated by theophylline, a substrate for the P450 cytochrome CYP1A2. It was reported that the elimination half-lives of theophylline ranged between 9 and 18 hours in term infants who are 6 to 12 weeks old. [38]. The dramatic alterations in theophylline plasma clearance occurring between 30 weeks (approximately 10 ml/h/kg) and 100 weeks (approximately 80 ml/h/kg) of postconceptional age, is primarily the result of age-dependent differences in metabolism of theophylline by CYP1A2 [39].

When administered intravenously, midazolam clearance reflects the CYP3A activity in the liver. The clearance and thus hepatic CYP3A activity is markedly lower in neonates less than 39 weeks of gestation (1.2 ml/kg/min) and greater than 39 weeks of gestation (1.8 ml/kg/min) relative to clearance of 9.1 ±3.3 ml/kg/min observed in infants greater than 3 months old. These data suggest that CYP3A activity increases approximately five fold over the first 3 months of life [40].

In addition to the P450 cytochromes, apparent age dependence exists for several phase II enzymes that are of quantitative importance for drug biotransformation. For example, the pharmacokinetics of selected substrates for UGT2B7 (e.g. lorazepam, morphine, naloxone) support a marked reduction in the level of activity for this isoform around the birth (approximately 10 to 20 % of the levels in adults), with attainment of competence equivalent to that in adults between 2 months and 3 years of age [41, 42].

Using published literature a children's pharmacokinetic database has been compiled which compares pharmacokinetic parameters between children and adults for 45 drugs. These comparisons indicate that premature and full-term neonates tend to have 3 to 9 times longer half-life than adults for the drugs included in the database. This difference disappears by 2-6 months of age. Beyond this age, half-life can be shorter than in adults for specific drugs and pathways [43]. The range of neonate/adult half – life ratios exceeds the 3.16-fold factor commonly ascribed to interindividual pharmacokinetic variability. Pharmacokinetics of xenobiotics can differ widely between children and adults due to physiological differences and the immaturity of the enzyme system and clearance mechanisms. This make extrapolation of adult dosimetry estimates to children uncertain, especially at early postnatal ages [43].

Such data suggest the importance of the study of targeted pediatric populations versus the entire pediatric population, to design of age (developmentally) – appropriate drug dosing regimens.

2.5. The Role of P-Glycoprotein and ABC-Transporters in Drug Metabolism and Drug-Drug Interactions

In addition to P450 enzymes, transporters play an important role in drug disposition. It is possible that drug-drug interactions at the site of transporters alter the plasma concentration-time profiles. Transporters mediate the membrane transport of a great number of drugs and endogenous compounds. The number of binding sites of transporters for drugs is limited, so the transport process is saturated at concentrations higher than the Km value. When drugs share the same binding sites of transporters, drug-drug interactions may occur depending on their pharmacokinetic properties. Interactions involving membrane transporters in organs of elimination (liver, kidney) and absorption (intestine) alter blood concentration time profiles of drugs.

Transporters can be classified into several families: secondary or tertiary active transporters (organic cation transporter, OCT; organic anion transporting polypeptide family, OATP; organic anion transporter, OAT; peptide transporter; sodium phosphate co transporter) and primary active transporters (P-glycoprotein, Pgp; multidrug resistance associated protein 1,MRP1; canalicular multispecific organic anion transporter, cMOAT/MRP2/cMRP; MRP3) [44].

Transport proteins mediate the translocation of specific molecules across various membranes. The translocation of their substrates can be either primary active using ATP hydrolysis as an energy source or secondary active using an existing cellular electrochemical gradient. Examples are the ATP-binding cassette transporters (ABC-transporters) or the solute carrier (SLC), respectively. The ABC-binding cassette transporters are a large and diverse superfamily of proteins comprising around fifty members with many and varied functions. Now a consistent nomenclature has been introduced, based on the sequence homology between these proteins. In this system the ABC genes are grouped into seven subfamilies, based on the similarity in the gene structure, order of the domains and sequence homology in the two nucleotide binding domains (NBDs) and two transmembrane domains (TMDs) (ABCA ABCB ABCC, ABCD, ABCE, ABCF, ABCG, each of them having different number of members, known also with different common names) [45,46,47].

One of the most important members is P-glycoprotein (ABCB1) known also as MDR1, a protein over expressed in

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