**VARIOUS FACTORS AFFECTING PHARMACOKINETICS**

**ABSTRACT**

Pharmacokinetics plays a pivotal role in the progression of drug development, focusing on how the body interacts with a drug. This fundamental aspect holds paramount importance in comprehending the drug's mode of operation. As a drug traverses the systemic circulation via diverse pathways like oral ingestion or parenteral introduction, it navigates through distinct stages from its point of entry to eventual elimination. These stages encompass absorption, distribution, metabolism, and excretion, collectively culminating in the determination of the drug's physiological impact.For some prodrugs, these processes are essential as they convert into their active forms during this journey. Many factors influencing the drug's behaviour depend on pharmacokinetic parameters. In this study, we will delve into the effects of different factors on these parameters, encompassing changes in absorption, distribution, metabolism, and excretion.

For some prodrugs, these processes are essential as they convert into their active forms during this journey. Many factors influencing the drug's behaviour depend on pharmacokinetic parameters. In this study, we will delve into the effects of different factors on these parameters, encompassing changes in absorption, distribution, metabolism, and excretion.

Within this chapter, we will explore various factors, including genetic influences, that play a role in shaping pharmacokinetic parameters. Understanding these factors is crucial for optimizing drug efficacy and safety during the drug development process.

Top of Form

**INTRODUCTION**

Pharmacokinetics, derived from "pharmakon" meaning "drug" and "kinetikos" meaning "moving or putting in motion," constitutes a crucial branch of pharmacology focused on understanding the fate of substances introduced into a living organism. These substances encompass a wide range of chemicals, including pharmaceutical agents, pesticides, food additives, cosmetics, and more.

The primary objective of pharmacokinetics is to investigate the changes that occur in the drug's behavior within the body. This encompasses the analysis of the chemical substance's metabolism from the time of administration until complete excretion. In essence, pharmacokinetics explores what the body does to the drug, while pharmacodynamics examines what the drug or chemicals do within the body. Together, these factors significantly influence the drug's dosing regimen, potential benefits, and side effects.

The branch of pharmacokinetics specifically delves into how the host's body processes the chemical substance following its administration. This involves processes such as absorption and distribution, metabolism by enzymes like cytochrome P450 or glucuronosyl enzymes, and the routes through which the changed form of the drug is excreted from the body.

The properties of drugs related to pharmacokinetics are significantly impacted by the route of administration and the dose or concentration of the administered drug, which can affect the absorption rate. Key processes involved in pharmacokinetics include:

* Liberation: The mechanism by which a drug substance is released from its formulation.
* Absorption: The process through which the substance enters the systemic circulation.
* Distribution: The distribution of drug substances among the body's fluids and tissues.
* Metabolism (or biotransformation, or inactivation): This process involves the identification of foreign substances present in the body and their irreversible conversion from parent compounds into metabolites.
* Excretion: This mechanism facilitates the elimination of drug substances from the body.

In this chapter, we will focus on exploring the various factors responsible for changes in the pharmacokinetics of drugs, with particular attention to their absorption, distribution, metabolism, and excretion patterns.

Top of Form

In some cases, certain drugs may irreversibly deposit in tissues. The elimination process involves two phases: metabolism and excretion. Understanding the dynamics of these phases is essential to comprehend substance kinetics. Several factors play a crucial role in this understanding, including:

* Excipient properties.
* Description of biological membranes and the processes by which substances cross them.
* Enzyme reactions associated with the inactivation of active drug molecules.

Information obtained through clinical pharmacokinetics provides valuable insights for the effective and proficient use of drugs and medicine by healthcare professionals.

In this chapter, we will focus on the various factors responsible for changes in pharmacokinetics, as well as the impact of genetic variation on pharmacokinetics.

Top of Form

**FACTORS AFFECTING ABSORPTION**

Gastrointestinal tract absorption is a complex process influenced by both its rate and extent. GI surgery can bring about changes in the anatomy and physiology of the gastrointestinal tract, leading to alterations in crucial variables related to drug absorption. For certain drugs like phenytoin, digoxin, and specific oral contraceptives, the rate of absorption is notably low, but the precise reasons behind this reduced absorption remain unknown. If gastric emptying time or pH is altered due to surgery, it can further reduce the rate of drug absorption. As a result, the specific variable that holds more significance in determining therapeutic effects remains inconclusive.

Incomplete absorption of several drugs has been observed in conditions affecting the small bowel, such as jejunoileal bypass (JIB) and short bowel syndromes following small bowel resection. However, no definitive evidence establishes a direct relationship between this incomplete absorption and altered GI structure. It is hypothesized that any malabsorption resulting from surgical procedures can be attributed to reductions in surface area and metabolism in the lumen of the gastrointestinal tract, variations in intestinal transit time due to the shortened length of the intestine, and changes in the gut's anatomy and physiology. Further research is needed to fully understand the intricate interplay between GI surgery, drug absorption, and therapeutic outcomes.

**Drugs affecting Absorption**

Under normal circumstances, the absorption of phenytoin is slow and varies in extent. However, in cases where malabsorption occurs, it is often due to a decrease in intestinal transit time caused by the shortened length of the intestine. For instance, a patient with obesity is prescribed with oral phenytoin 300mg and phenobarbital 90mg daily to manage seizures.

Digoxin's bioavailability varies among healthy volunteers, ranging from 60% to 80% for tablets, 70% to 85% for elixirs, and 90% to 100% for use solution-filled gelatin capsules. The primary site of digoxin absorption is the proximal part of the small intestine, with a smaller extent of absorption occurring in the distal part of the small intestine.

**GI disease affecting Absorption**

GI diseases do not typically cause irreversible alterations in the anatomy of the gastrointestinal tract. However, GI surgery can lead to changes in factors such as gastric emptying time, gastric and intestinal lumen pH, and the structure of the absorption surface area. Inflammatory bowel disease (IBD) and coeliac disease, on the other hand, can have variable effects on drug absorption by influencing the mucosal lining of the intestine or the gastric emptying time.

Some of these factors are attributed to inherent population variability, and the effects may vary with changes in the disease process. Thus, the interplay between GI surgery, GI diseases, and drug absorption is complex and can impact the therapeutic outcomes in different ways.

**Bile salts:**

The presence of bile plays a crucial role in enhancing the bioavailability of drugs by promoting their dissolution and solubility. Bile salts, through a process called micellar solubilization, increase the solubility of drugs. This mechanism reduces the interfacial energy barrier between the solid drug and the dissolution media, leading to improved wetting of the solid drug. As a result, the rate of drug dissolution increases, effectively increasing the drug's surface area available for absorption. This process contributes significantly to the improved bioavailability of the drugs.

**Gastric emptying and Intestinal transit time**

Drug absorption primarily depends on two key parameters: gastric emptying and gastrointestinal (GI) transit time. The plasma concentration profile of orally administered drugs is influenced by the rate at which the stomach empties its contents, while the intestinal transit rate also plays a crucial role in drug absorption. The intestinal transit time determines how long the drug remains in the intestine, and this residence time is vital for absorption, especially for drugs that exhibit variations in absorbability at different sites within the GI tract. As a result, residence time becomes a critical factor influencing drug absorption for certain medications.[1]

**Food Effect**

The presence of food significantly impacts drug oral bioavailability. It induces physiological changes through two main mechanisms: increasing gastric pH or slowing gastric emptying rate. The fed and fasted states can alter the pH and affect the dissolution and absorption processes of weakly acidic and basic drugs.

After a meal, the elevation of gastric pH enhances the dissolution of weak acids in the stomach, but conversely, it inhibits the dissolution of weak bases. This can have varied effects on drug absorption depending on the drug's acidic or basic properties.

Furthermore, the prolonged retention of a drug in the stomach increases the proportion of the drug that dissolves before passing into the small intestine, which is the primary site of absorption. This extended retention can lead to altered drug absorption kinetics.

Overall, the presence of food plays a critical role in modulating drug absorption, affecting factors like gastric pH, dissolution, and gastric emptying rate, and subsequently impacting the drug's oral bioavailability.

**Binding of drug to the Plasma Protein**

The cell membrane allows the free and unbound form of a drug to cross it. Within the plasma, two types of plasma proteins, albumins, and globulins, bind with drugs. The pH of the plasma plays a crucial role in determining the amount and type of binding sites available for drugs.

Neutral and acidic drugs predominantly bind with albumins, while basic drugs tend to bind with globulins. Even minor changes in the protein binding can lead to significant alterations in the total amount of unbound drug, especially for drugs with high protein binding characteristics.

Various factors can impact protein binding, including acute infective or inflammatory processes, pathogenic conditions, or reduction in synthetic capacity due to liver impairment. These conditions can result in a reduced amount of albumin, consequently affecting the proportion of unbound drugs in the plasma. Understanding these factors is essential for optimizing drug efficacy and safety during medical treatment.[3]

p Glycoprotein:

P-glycoprotein (P-gp), an ATP-binding cassette (ABC) membrane transporter, is a significant human efflux transporter. This transporter, encoded by the ABCB1 gene, is located on the apical side of various barriers in the small intestine, where it plays a crucial role in regulating the movement of xenobiotics in and out of cells. ABCB1 acts as a checkpoint, controlling the entry of drugs, but it also contributes to the excretion of drugs from cells.

P-gp is predominantly present in the apical membranes of the small intestine [7-8], and its presence significantly lowers the bioavailability of numerous drugs. Additionally, it is often co-expressed with proteins of cytochrome P450 3A, forming a defense mechanism against various compounds. This defense mechanism involves altering the lipophilicity of a compound and converting it into more hydrophilic and less permeable derivatives, which aids in the elimination of potentially harmful substances.

Interestingly, P-gp is highly expressed in the duodenum and jejunum compared to the liver, further highlighting its essential role in regulating drug absorption and disposition in the small intestine. Understanding the functions and expressions of P-gp is vital for optimizing drug therapy and predicting potential drug interactions.[9].

**FACTORS AFFECTING DISTRIBUTION**

Once a drug enters the systemic circulation, it undergoes distribution to reach its target sites and exert its therapeutic effects. The distribution of the drug within tissues is influenced by factors such as blood permeability to the tissues, drug solubility, and tissue uptake.

In the human body, water constitutes around 50% to 70% of total body weight, with variations in aged individuals and women who may have a lower percentage due to reduced lean body mass. The body's water content is divided into four compartments: intracellular fluid (40% of total body water), plasma (5%), interstitial fluid (15%), and transcellular fluid (1% of body weight). Transcellular fluid includes cerebrospinal, intraocular, peritoneal, pleural, and synovial fluids, as well as digestive tract secretions.

For drugs to reach these various fluid compartments and tissues from the plasma, they must traverse epithelial barriers while maintaining equilibrium. Drug molecules can exist in both bound and unbound forms and in charged and uncharged forms within different body compartments.

The distribution of drugs is influenced by several factors, including the ability of drug molecules to traverse cell membranes, the ratio of bound and unbound drug in different compartments, pH partitioning, and the fat-to-water partition. These factors collectively determine the distribution of the drug within the body and play a critical role in its pharmacological effects. Understanding drug distribution is crucial for optimizing drug therapy and ensuring successful treatment outcomes.[10]

Top of Form

**Volume of distribution and different compartment models Volume of distribution**

Volume of distribution (Vd) is a theoretical concept that describes how a drug distributes within the body. It represents the hypothetical volume of fluid that would be needed to contain the entire amount of drug in the body at the same concentration as present in the plasma. Drugs that are highly bound to plasma proteins tend to have a smaller volume of distribution, while those that redistribute quickly and bind to tissues have a larger volume of distribution.

Mathematical models are employed to analyze pharmacokinetic processes and predict the timing of drug action. The single-compartment model assumes that the drug is uniformly distributed throughout both plasma and other tissues, treating them as a single compartment. From there, the drug is eliminated in a washout manner. The simplicity of the single-compartment model makes it useful for describing drug behavior.

In contrast, multi-compartment models are employed to understand how drugs are taken up from the plasma by different tissues throughout the body. These models provide reliable information on the flow rates to these tissues, helping to comprehend drug distribution more comprehensively. The use of these models allows for a more in-depth analysis of drug pharmacokinetics and contributes to a better understanding of drug effects in the body.[11].

**Distribution of drugs to the foetus**

The placental chorionic villi are composed of trophoblastic cells surrounding fetal capillaries. The placental syncytiotrophoblast and fetal capillary membranes merge to form a single lipid barrier that separates maternal and fetalblood. This lipid barrier allows lipid-soluble substances to pass more easily than water-soluble substances, particularly those with a molecular weight exceeding 500. Compared to the blood-brain barrier, the placental membrane is less selective, enabling moderately lipid-soluble molecules to cross more easily.

The rate at which drugs equilibrate across the placenta depends on placental blood flow and the drug concentration gradient between maternal and fetal blood. The pH of fetal blood is lower than that of the mother, which can impact drug transfer across the placenta in two ways: first, altering the degree of ionization of drugs in fetal blood. Weak bases with a pKa higher than physiological pH (e.g., local anesthetics) become more ionized in the lower pH of the fetus, possibly leading to ion trapping. In this situation, ionized drugs in fetal capillary blood cannot return across the placenta, and if the fetus becomes even more acidic, it could result in toxic levels of the drug in the fetus.

Second, pH differences between maternal and fetal blood can influence the relative protein binding of drugs across the placenta, thus altering the free drug concentration gradient. Higher protein binding in the fetus increases drug transfer from mother to fetus, while higher protein binding in the mother reduces drug transfer from mother to fetus. The ratio of albumin and globulin may also differ between the mother and fetus, especially in conditions like pre-eclampsia, where maternal serum albumin levels are low. This can increase the transfer of neutral and acidic drugs across the placenta from mother to fetus.

Overall, understanding the complexities of drug transfer across the placenta is crucial for optimizing drug therapy during pregnancy and ensuring the safety of both mother and fetus.[12].

The placenta plays a vital role in the transfer of drugs between the mother and the fetus during pregnancy. Understanding the factors that influence drug transfer across the placenta is crucial for ensuring the safety and well-being of both the mother and the developing baby.

One important factor to consider is the placental membrane, which acts as a barrier between maternal and fetal blood. This lipid barrier allows lipid-soluble substances to pass more easily than water-soluble substances, making it relatively permeable to certain molecules. However, it is less selective compared to the blood-brain barrier, allowing moderately lipid-soluble molecules to cross more easily.

The rate at which drugs equilibrate across the placenta depends on placental blood flow and the concentration gradient between maternal and fetal blood. It's important to note that the pH of fetal blood is lower than that of the mother, which can have implications for drug transfer.

The difference in pH can impact the ionization of drugs in fetal blood. Weak bases with a pKa higher than the physiological pH of the fetus may become more ionized, potentially leading to ion trapping. In such cases, ionized drugs in fetal capillary blood cannot return across the placenta, which could result in toxic levels of the drug in the fetus if the fetus becomes even more acidic.

Another important consideration is the effect of pH differences on protein binding of drugs across the placenta. Higher protein binding in the fetus increases drug transfer from mother to fetus, while higher protein binding in the mother reduces drug transfer. Additionally, the ratio of albumin and globulin may vary between the mother and fetus, particularly in conditions like pre-eclampsia where maternal serum albumin levels are low. This can increase the transfer of neutral and acidic drugs across the placenta.

In conclusion, understanding the complexities of drug transfer across the placenta is essential for optimizing drug therapy during pregnancy. Healthcare providers must carefully consider factors such as the lipid barrier of the placental membrane, placental blood flow, pH differences, and protein binding. By doing so, they can ensure the safety and well-being of both the mother and the developing fetus throughout the course of pregnancy.

**Multiple Drug Transporter**

The placental barrier between the maternal and fetal blood is a critical junction that plays a crucial role in drug transport. This barrier consists of various transporters, including P-glycoprotein, which facilitate the movement of multiple drugs between the maternal and fetal compartments. [13].These transporters play a significant role in safeguarding the fetus against drugs that the mother may take during pregnancy. They act as protective barriers, regulating the transfer of drugs from the maternal circulation to the fetal circulation, thereby helping to maintain the well-being of the developing fetus.[14].

P-glycoprotein at the blood-brain barrier serves as a defense mechanism against drugs that may impact the brain. It acts as a protective barrier, preventing the diffusion of certain drugs into the central nervous system (CNS) [15]. For instance, drugs like verapamil or downregulation of P-glycoprotein following inflammatory stimuli can lead to the inhibition of P-glycoprotein, resulting in a gradual increase in the transport of typical substrates across the blood-brain barrier. This alteration in P-glycoprotein function may influence drug penetration into the CNS and potentially affect the brain's response to these substances. [16]

**Liver Microsomes affecting the Drug metabolism**

Starvation can lead to notable changes in liver structures, particularly affecting drug metabolism, especially in liver microsomes. Liver tissue from fasted animals shows distinct differences compared to normal conditions. During starvation, there is a rapid decrease in cytoplasmic basophilia, leading to the loss of ergastoplasm in most hepatic cells. The overall structure also undergoes significant changes in dispersion.

These cellular alterations in liver structure are believed to be caused by a reduction in the amount of ergastoplasm and changes in microsome subunits, which may impact specific drug metabolisms mediated by liver microsomes. Many drugs undergo metabolism by enzymes present in liver microsomes. In fasted animals, there is heightened sensitivity to drugs due to deficiencies in these enzymes.

Several drug pathways have been studied in relation to this factor. Some of these include side-chain oxidation of hexobarbital, N-dealkylation of pyramidon, hydroxylation of the aromatic ring of acetanilide, oxidation of the ring sulfur of chlorpromazine, reduction of the aromatic nitro-group of p-nitrobenzoic acid, and reduction of the aromatic azo-group of neoprontosil.

In summary, starvation-induced changes in liver structures can significantly impact drug metabolism, leading to altered responses to various drugs in fasted animals. Understanding these effects is important for considering drug dosages and responses in clinical settings, especially when dealing with individuals experiencing nutritional deficiencies or undergoing fasting.Top of Form[17].

**FACTORS AFFECTING METABOLISM**

**Effect of Drugs on Gut Flora Metabolism:**

Studies have shown that the use of antibiotics, both in animals and humans, particularly when administered orally, can impact certain components of gut microflora. The extent of suppression largely depends on factors like the specific antibiotic used, its dosage, and the resistance of colonic organisms.

Researchers have utilized combinations of antibiotics to create "pseudo-germ-free" animals for short periods. These animals have provided valuable evidence regarding the role of gut microflora in the metabolism and toxicity of xenobiotics (foreign substances). For instance, experiments with rats demonstrated that the drug salicylazosulfapyridine's reduction was inhibited by neomycin treatment. Similarly, the conversion of p-nitrobenzoic acid to its amino derivative and the demethylation of methylmercury to mercuric mercury were significantly reduced in rats after administering mixtures of antibiotics that completely eliminated gut microflora.

In the case of methylmercury, antibiotic treatment was found to increase the neurotoxicity of the mercurial due to the suppression of the detoxification action of gut flora. These findings highlight the crucial role played by gut microflora in the metabolism and detoxification of xenobiotics and underscore the importance of considering antibiotic usage's potential impact on gut health and drug metabolism[18].

**Microsomal Enzyme Expression:**

The enzyme family known as Cytochrome P450 (CYPs) plays a significant role in the oxidative biotransformation of various drugs. This process is essential in drug metabolism, making CYPs highly important in the field of clinical pharmacology [19-21]. Loss-of-function polymorphisms in CYP genes primarily affect splicing and expression, rather than transcription [22]. On the other hand, gain-of-function variants include copy number variants (CNVs) where there is an increase in the number of functional gene copies in CYP2D6 and CYP2A6 [23]. Additionally, gain-of-function variants also involve promoter variants (e. . in CYP2B6, CYP2C19) and amino acid variants that enhance substrate turnover (e. . in CYP2B6, CYP2C8).

Loss-of-function variants result in reduced drug clearance and higher plasma concentrations, while gain-of-function variants lead to increased drug clearance and lower drug concentrations. However, in the case of prodrugs, the opposite effect is expected. Gain-of-function variants enhance activation, while loss-of-function variants reduce activation. This consideration is crucial for evaluating the pharmacological activity or toxicity of metabolites, such as the CYP2D6-dependent formation of morphine from codeine.

**Epigenetic influences on drug metabolism:**

Epigenesis refers to the phenomenon where variations in gene function are not solely based on DNA sequence changes. Two essential mechanisms involved in epigenesis are DNA methylation and histone protein modification. DNA methylation plays a crucial role in controlling gene expression, while histone modifications influence the accessibility and transcriptional activity of chromatin within cells.

Epigenetics also encompasses gene regulatory mechanisms involving microRNAs (miRNAs). These epigenetic processes are reversible and may be specific to certain tissues, influenced by host factors such as sex, age, and environmental factors.

The impact of epigenetic processes on pharmacologically relevant genes and drug response is a relatively new area of research, and it holds significant potential for understanding how individual genetic makeup, as well as environmental influences, can affect drug metabolism and efficacy. This evolving field of study promises to shed light on personalized medicine and optimize drug therapies for individual patients. [24].

MiR-27b, a microRNA, is involved in the regulation of the vitamin D receptor (VDR) and CYP3A4, a key enzyme responsible for drug metabolism. Through its action, miR-27b exerts both indirect and direct regulatory effects on CYP3A4. The vitamin D receptor, a transcriptional regulator of CYP3A4, is also under the influence of miR-27b, adding to the complexity of miRNA-mediated regulation of CYP3A4. [25].

**Nongenetic host factors:**

The sex of the host significantly influences several pharmacokinetically important parameters, such as body weight, fat distribution, liver blood flow, and the expression of drug metabolizing enzymes and transporters [26-27]. A recent genome-wide gene expression study conducted on 112 male and 112 female livers revealed that more than 1300 genes showed significant differences in mRNA expression between the sexes [28]. Interestingly, 75% of these genes were found to be expressed at higher levels in females. Among them, 40 ADME/ADME-related genes, including CYP1A2, CYP3A4, and CYP7A1, were notably abundant in females, while CYP3A5, CYP27B1, and UGT2B15 were expressed more in males.

Clinical studies have further demonstrated that women tend to metabolize drugs more rapidly than men, particularly in the case of substrates of the major drug metabolizing cytochrome P450, CYP3A4. Examples of such substrates include antipyrine, alfentanil, erythromycin, midazolam, and verapamil. These findings highlight the significant impact of sex-related differences on drug metabolism and underscore the importance of considering sex as a crucial factor in drug development and personalized medicine approaches. [29].

Age plays a crucial role in drug metabolism capacity, especially during the early and late stages of life when drug metabolism abilities tend to be lower. In neonates, drug metabolism is significantly affected by the immaturity of various enzyme systems, including cytochromes P450. These factors contribute to differences in drug processing and response in individuals at different life stages. [30-31].

**Presence of P Glycoprotein:**

P-gp, a membrane transporter, is also found at the canalicular site of hepatocytes, but its presence is approximately seven times lower compared to small-intestinal enterocytes [32]. The expression of hepatic P-gp varies significantly among individuals, showing differences of up to 50 times [33]. This variability in P-gp expression contributes to substantial differences in the bioavailability of a wide range of drugs. The varying levels of hepatic P-gp play a significant role in drug disposition and response, leading to diverse drug effects and outcomes among different individuals.

**FACTORS AFFECTING EXCRETION**

After the drug enters the systemic circulation and undergoes distribution, the body initiates several mechanisms to eliminate it. Excretion can occur through various pathways, involving biotransformation into metabolites (active or inactive) and/or elimination by specific organs. The kidneys and liver are typically the primary excretory organs, responsible for removing drugs and their metabolites from the body. In addition to these major routes, other excretion pathways include exhaled breath, saliva, sweat, tears, breast milk, and substances like hair and nails. These diverse excretion routes contribute to the overall elimination process, ensuring the removal of drugs and their byproducts from the body, thereby concluding the drug's journey through the system. [34].

In the kidney, drug transport is facilitated by specific transporters located on both the basolateral and apical membranes of renal proximal tubule cells (PTCs). Basolateral uptake transporters, such as OAT1, OAT3, and OCT2, are responsible for transporting drugs from the blood into the renal PTCs. On the other hand, apical efflux transporters, including MRP2, MRP4, and P-gp, are responsible for transporting drugs from the renal PTCs into the urine for eventual excretion.

Moreover, there are uptake transporters located on the apical membrane of proximal tubules, like OCTN1 and OCTN2, which play a role in reabsorbing xenobiotics that have been filtered through the glomeruli back into the tubule cells. Conversely, basolateral efflux transporters such as MRP1, MRP3, and MRP6 facilitate the transport of these reabsorbed chemicals back into the blood.

These intricate transport systems in the kidney ensure the efficient elimination of drugs and their metabolites from the body via urine, contributing to the overall drug excretion process.

**Renal Dysfunction**

In the eleventh edition of Goodman & Gilman's The Pharmacological Basis of Therapeutics, there is a comprehensive pharmacokinetic data table in Appendix II, containing information on approximately 300 drugs. Surprisingly, out of these drugs, only 22% are eliminated through renal excretion in their unchanged form by at least 50%. The majority of drugs undergo biotransformation and other routes of elimination before being excreted from the body. This data highlights the complex and diverse pathways involved in drug elimination and emphasizes the importance of understanding drug metabolism for effective therapeutic use. [35].Renal dysfunction not only affects the excretion of unchanged drugs or their metabolites but also has a significant impact on the distribution, transport, and biotransformation of drug substances. The impaired kidney function can lead to altered pharmacokinetic processes, influencing how drugs are distributed and processed within the body. Understanding these changes is crucial for adjusting drug dosages and ensuring safe and effective drug therapy in patients with renal impairment. Renal dysfunction can be classified based on the underlying causes, and it manifests with distinct histological changes in glomeruli and tubules. The intact nephron hypothesis posits that in diseased nephrons, all components of the nephron are affected equally, implying that the functional impairment extends throughout the entire nephron. This hypothesis highlights the widespread impact of renal dysfunction on various aspects of kidney function, including both glomerular and tubular functions. Understanding the histological changes and functional alterations in diseased nephrons is vital for comprehending the complexities of renal disorders and devising appropriate treatment strategies.[36In addition to the intrarenal pathways of excretion, such as filtration, secretion, and reabsorption, the estimation of excretory function loss in a diseased kidney is commonly based on the measurement of glomerular filtration rate (GFR). However, in cases of acute renal failure, it is important to recognize that glomerular filtration and tubular secretion via the anionic and cationic pathways are not equally affected. These differential impacts on renal functions contribute to the complexity of assessing kidney function during acute renal failure and require careful consideration in clinical management.

**Effect of dialysis on drug excretion**

Patients with end-stage renal disease (ESRD) have several treatment options to manage their condition effectively. Among these options are hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), and automated peritoneal dialysis. These therapies play a crucial role in providing renal replacement and supporting the overall health and well-being of individuals with ESRD. Each method has its benefits and considerations, offering patients different choices based on their specific needs and preferences. Through these treatments, patients can improve their quality of life and enhance their long-term prognosis. [37, 38]. In the management of end-stage renal disease (ESRD), high-flux dialysis and hemodiafiltration stand as important renal replacement therapies. These treatments play a pivotal role in providing patients with ESRD the much-needed support for their compromised kidney function. By utilizing advanced filtration techniques, high-flux dialysis and hemodiafiltration help in effectively removing waste products and excess fluids from the bloodstream, assisting patients in maintaining a better balance of essential electrolytes and fluids. These therapies significantly contribute to enhancing the overall well-being and prognosis of individuals facing the challenges of ESRD.[39, 40The primary objective of these procedures is to efficiently eliminate toxic waste products that tend to accumulate in patients with end-stage renal disease (ESRD. Additionally, they are effective in removing drugs and active drug metabolites from the body. As a result, dosage adjustments may be required for patients undergoing these dialysis techniques to ensure proper medication management and optimize therapeutic outcomes. By effectively cleansing the blood and helping to regulate drug levels, these procedures play a critical role in supporting the overall health and well-being of ESRD patients. [41.42]. The extent to which a drug is eliminated from the body during dialysis depends on two factors: the proportion of the drug's total elimination that is accounted for by dialysis and the proportion of the drug that is lost through all elimination pathways. The combination of these two fractions determines the amount of drug that will be removed from the body during the dialysis procedure. Accurately assessing these proportions is crucial for understanding the overall impact of dialysis on drug elimination and ensuring effective management of drug therapy in patients undergoing dialysis.[41].

**Renal Transporter Presence**

While the liver is indeed a significant organ for drug excretion, transporters in tubular cells within the kidney also play a crucial role. One such transporter is the ABCB1 transporter, also known as p-glycoprotein, which is located on the luminal side of these cells. This transporter actively facilitates the secretion of lipophilic drugs and other xenobiotics from the blood into the tubules for eventual elimination through urine. The presence of ABCB1 in the kidney contributes to the efficient excretion of various substances, making it an important component of the overall drug elimination process. [43]. In cancerous kidney tissue, the presence of ABCB1 was observed to be lower in comparison to normal kidney tissue. This reduction in ABCB1 expression may be attributed to the diminished functionality of tubular cells in the cancerous tissue. The altered cellular environment and disrupted cellular processes in cancerous kidney tissue may lead to changes in the expression and activity of transporters like ABCB1, potentially affecting the drug transport and excretion mechanisms in these tissues. Understanding these differences in transporter expression is essential for developing effective treatment strategies and optimizing drug therapies in patients with kidney cancer.[44]

**Genetic Variation in the Renal Transporter**

The organic anion transporting polypeptides (OATPs) are essential membrane transport proteins responsible for facilitating the sodium-independent transport of a wide range of amphiphilic organic acids. These transporters belong to a family with 12 putative transmembrane domains and are present in various barrier organs such as the intestine, liver, kidney, and brain. Their vital role in drug absorption, distribution, and excretion makes them crucial players in regulating the pharmacokinetics and overall disposition of drugs within the body. By mediating the transport of diverse organic compounds, OATPs play a significant role in the efficient uptake and elimination of drugs, impacting drug bioavailability and therapeutic efficacy. [45]

Central to the landscape of renal secretion for small organic cations, including metformin, is the transporter OCT2 (SLC22A2), an indispensable player. Just as with its counterpart OCT1, the genetic landscape of OCT2 unveils a multitude of variations across diverse populations, spanning Caucasians, African–Americans, Asian–Americans, Mexican–Americans, and Pacific Islanders. Within the SLC22A2 gene, a total of 28 genetic variations have been meticulously documented among these ethno-cultural groups. This rich tapestry of genetic diversity bears the potential to intricately shape the performance and function of OCT2, consequently wielding an impact on the renal clearance and disposition of drugs that interface with this transporter.[46]

**CONCLUSION**

In the human body, drugs often undergo various changes before they can reach their intended site of action. Unfortunately, therapeutic failure and drug toxicity are factors that can sometimes go unnoticed by doctors. These issues may arise due to alterations in drug pharmacokinetics, which can significantly impact the effectiveness and safety of drug therapy.

This study aims to explore the multitude of factors responsible for changes in drug pharmacokinetics, which can potentially lead to drug therapy failure. Among these factors, epigenetics plays a significant role, and both genetic and non-genetic elements are thoroughly investigated in this comprehensive review.

By understanding the complex interplay of these factors, healthcare professionals can enhance their ability to identify potential issues in drug therapy and optimize treatment regimens for better patient outcomes. This research provides valuable insights into the diverse influences on drug pharmacokinetics, helping to pave the way for more precise and effective drug administration.

**REFERENCES**

[1] Song, N. N., Zhang, S. Y., & Liu, C. X. (2004). Overview of factors affecting oral drug absorption. *Asian J Drug MetabPharmacokinet*, *4*(3), 167-176.

[2] Lipka, E., & Amidon, G. L. (1999). Setting bioequivalence requirements for drug development based on preclinical data: optimizing oral drug delivery systems. *Journal of controlled release*, *62*(1-2), 41-49.

[3] Affrime, M. and Reidenberg, M.M.: The protein binding of-some drugs in plasma from patients with alcoholic liver disease. European Journal of Clinical Pharmacology 8: 267-269 (] 975).

[4] Schinkel AH, Wagenaar E, Mol CA, van Deemter L (1996) P-glycoprotein in the blood–brain barrier of mice influences the brain penetration and pharmacological activity of many drugs. J Clin Invest 97:2517–2524

[5] Terao T, Hisanaga E, Sai Y, Tamai I, Tsuji A (1996) Active secretion of drugs from the small intestinal epithelium in rats by P-glycoprotein functioning as an absorption barrier. J Pharm Pharmacol 48:1083–1089

[6] Zhang Y, Benet LZ (2001) The gut as a barrier to drug absorption: combined role of cytochrome P450 3A and P-glycoprotein. ClinPharmacokinet 40:159–168

[7] Canaparo R, Finnstrom N, Serpe L, Nordmark A, Muntoni E, Eandi M, Rane A, Zara GP (2007) Expression of CYP3A isoforms and P-glycoprotein in human stomach, jejunum and ileum. ClinExpPharmacolPhysiol 34:1138–1144

[8] Thorn M, Finnstrom N, Lundgren S, Rane A, Loof L (2005) Cytochromes P450 and MDR1 mRNA expression along the human gastrointestinal tract. Br J ClinPharmacol 60:54–60

[9] von Richter O, Burk O, Fromm MF, Thon KP, Eichelbaum M, Kivisto KT (2004) Cytochrome P450 3A4 and P-glycoprotein expression in human small intestinal enterocytes and hepatocytes: a comparative analysis in paired tissue specimens. ClinPharmacolTher 75:172–183

[10] Lötsch, J., Skarke, C., Wieting, J., Oertel, B. G., Schmidt, H., Brockmöller, J., &Geisslinger, G. (2006). Modulation of the central nervous effects of levomethadone by genetic polymorphisms potentially affecting its metabolism, distribution, and drug action. *Clinical Pharmacology & Therapeutics*, *79*(1), 72-89

[11] Kharasch ED, Hoffer C, Whittington D, Sheffels P. Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. ClinPharmacolTher 2004;76:250-69.

[12] Chillistone, S., & Hardman, J. G. (2017). Factors affecting drug absorption and distribution. *Anaesthesia & Intensive Care Medicine*, *18*(7), 335-339.

[13] Young AM, Allen CE, Audus KL (2003) Efflux transporters of the human placenta. Adv Drug Deliv Rev 55:125–132

[14] Behravan J, Piquette-Miller M (2007) Drug transport across the placenta, role of the ABC drug efflux transporters. Expert Opin Drug MetabToxicol 3:819–830

[15] Fromm MF (2004) Importance of P-glycoprotein at blood-tissue barriers. Trends PharmacolSci 25:423–429

[16] Goralski KB, Hartmann G, Piquette-Miller M, Renton KW (2003) Downregulation of mdr1a expression in the brain and liver during CNS inflammation alters the in vivo disposition of digoxin. Br J Pharmacol 139:35–48

[17] Dixon, R. L., Shultice, R. W., &Fouts, J. R. (1960). Factors affecting drug metabolism by liver microsomes. IV. Starvation. *Proceedings of the Society for Experimental Biology and Medicine*, *103*(2), 333-335

[18] Rowland, I. R. (1988). Factors affecting metabolic activity of the intestinal microflora. *Drug metabolism reviews*, *19*(3-4), 243-261.

[19] Nelson, D. R. (2004). Cytochrome P450 nomenclature, 2004. Methods MolBiol 320, 1–10.

[20] Guengerich, F. P. (2008). Cytochrome P450 and chemical toxicology. Chem Res Toxicol 21, 70–83

[21] Zanger, U. M., & Hofmann, M. H. (2008). Polymorphic cytochromes P450 CYP2B6 and CYP2D6: recent advances on single nucleotide polymorphisms affecting splicing. ActaChimSlov 55, 38.

[22] Sadee, W., Wang, D., Papp, A. C., Pinsonneault, J. K., Smith, R. M., Moyer, R. A., et al. (2011). Pharmacogenomics of the RNA world: structural RNA polymorphisms in drug therapy. ClinPharmacolTher 89, 355–365.

[23] Johansson, I., &Ingelman-Sundberg, M. (2008). CNVs of human genes and their implication in pharmacogenetics. Cytogenet. Genome Res 123, 195–204.

[24] Ingelman-Sundberg, M., & Gomez, A. (2010). The past, present and future of pharmacoepigenomics. Pharmacogenomics 11, 625–627.

[25] Pan, Y. -Z., Gao, W., & Yu, A. -M. (2009). MicroRNAs regulate CYP3A4 expression via direct and indirect targeting. Drug MetabDispos 37, 2112–2117.

[26] Beierle, I., Meibohm, B., &Derendorf, H. (1999). Gender differences in pharmacokinetics and pharmacodynamics. Int J ClinPharmacolTher 37, 529–547

[27] Gandhi, M., Aweeka, F., Greenblatt, R. M., &Blaschke, T. F. (2004). Sex differences in pharmacokinetics and pharmacodynamics. Annu Rev PharmacolToxicol 44, 499

[28] Zhang, Y., Klein, K., Sugathan, A., Nassery, N., Dombkowski, A., Zanger, U. M., et al. (2011). Transcriptional profiling of human liver identifies sex-biased genes associated with polygenic dyslipidemia and coronary arte

[29] Cotreau, M. M., Von Moltke, L. L., & Greenblatt, D. J. (2005). The influence of age and sex on the clearance of cytochrome P450 3A substrates. ClinPharmacokinet 44, 33–60.

[30] Kinirons, M. T., &O'Mahony, M. S. (2004). Drug metabolism and ageing. Br J ClinPharmacol 57, 540–544

[31] Koukouritaki, S. B., Manro, J. R., Marsh, S. A., Stevens, J. C., Rettie, A. E., McCarver, D. G., et al. (2004). Developmental expression of human hepatic CYP2C9 and CYP2C19. J PharmacolExpTher 308, 965–974.

[32] von Richter O, Burk O, Fromm MF, Thon KP, Eichelbaum M, Kivisto KT (2004) Cytochrome P450 3A4 and P-glycoprotein expression in human small intestinal enterocytes and hepatocytes: a comparative analysis in paired tissue specimens. ClinPharmacolTher 75:172–183

[33] Schuetz EG, Furuya KN, Schuetz JD (1995) Interindividual variation in expression of P-glycoprotein in normal human liver and secondary hepatic neoplasms. J PharmacolExpTher 275:1011–1018

[34] Margherita Strolin Benedetti, Rhys Whomsley, ItaloPoggesi, Willi Cawello, François-Xavier Mathy, Marie-Laure Delporte, Peggy Papeleu& Jean-Baptiste Watelet (2009) Drug metabolism and pharmacokinetics, Drug Metabolism Reviews, 41:3, 344-390, DOI: [10.1080/10837450902891295](https://doi.org/10.1080/10837450902891295)

[35] Thummel KE, Shen DD, Isoherranen N, Smith HE (2006) Design and optimization of dosage regimens: pharmacokinetic data. In: Brunton LL, Lazo LL, Parker KL (eds) Goodman & Gilman’s The pharmacological basis of therapeutics, 11 edn. McGraw-Hill, New York, pp 1787–1888

[36] Bricker NS, Morrin PAF, Kime SW Jr (1997) The pathologic physiology of chronic Bright’s Disease: an exposition of the “intact nephron hypothesis”. J Am SocNephrol 8:1470–1476

[37] Woffindin C, Hoenich NA (1995) Hemodialyzer performance: a review of the trends over the past two decades. Artif Organs 19:1113–1119

[38] Gjessing J (2008) Studies on peritoneal dialysis. Kidney IntSuppl 108:S18–S25

[39] Fujimura T, Uchi Y, Fukuda M, Miyazaki M, Uezumi S, Hiyoshi T (2004) Development of a dialyzer with enhanced internal filtration to increase the clearance of low molecular weight proteins. J Artif Organs 7:149–153

[40] Lucchi L, Fiore GB, Guadagni G, Perrone S, Malaguti V, Caruso F, Fumero R, Albertazzi A (2004) Clinical evaluation of internal hemodiafiltration (iHDF): a diffusive-convective technique performed with internal filtration enhanced high-fluc dialyzers. Int J Artif Organs 27:414–419

[41] Rowland M, Tozer TN (1995) Clinical pharmacokinetics: concepts and applications, 3rd edn. Lippincott Williams & Wilkins, Philadelphia

[42] Matzke GR, Comstock TJ (2006) Influence of renal function and dialysis on drug disposition. In: Burton ME, Shaw LM, Schentag JJ, Evans WE (eds) Applied pharmacokinetics and pharmacodynamics: principles of therapeutic drug monitoring, 4th edn. Lippincott Williams & Wilkins, Philadelphia, pp 187–212

[43] del Moral RG, Olmo A, Aguilar M, O’Valle F (1998) P glycoprotein: a new mechanism to control drug-induced nephrotoxicity. ExpNephrol 6:89–97

[44] Haenisch S, Zimmermann U, Dazert E, Wruck CJ, Dazert P, Siegmund W, Kroemer HK, Warzok RW, Cascorbi I (2007) Influence of polymorphisms of ABCB1 and ABCC2 on mRNA and protein expression in normal and cancerous kidney cortex. Pharmacogenomics J 7:56–65

[45] Niemi M. Role of OATP transporters in the disposition of drugs. Pharmacogenomics 8(7), 787–802 (2007)

[46] Leabman MK, Huang CC, Kawamoto M et al. Polymorphisms in a human kidney xenobiotic transporter, OCT2, exhibit altered function. Pharmacogenetics 12(5), 395–405 (2002).