ClinicSearch

Clinical Endocrinology and Metabolism

Gudisa Bereda *

Open Access

Review Article

What The Body Does to A Drug: Pharmacokinetics

Gudisa Bereda *

Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia

Corresponding Author: Gudisa Bereda, Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia.

Received date: September 06, 2022; **Accepted date:** September 23, 2022; **Published date:** October 24, 2022.

Citation: Gudisa Bereda. (2022). What The Body Does To A Drug: Pharmacokinetics, *J.Clinical Endocrinology and Metabolism*, 1(2)
DOI: 10.31579/cem.2022/006

Abstract

Pharmacokinetics may be defined as the study of the dynamic movements of foreign chemicals (xenobiotics) during their passage through the body and as such encompass the kinetics of absorption, distribution, biotransformation/metabolism and excretion. Absorption is the process that brings a drug from the administration, e.g., tablet, capsule, into the systemic circulation. Bioavailability is the fraction of the originally administered drug that arrives in systemic circulation and depends on the properties of the substance and the mode of administration. It can be a direct reflection of medication absorption. Distribution describes how a substance is spread throughout the body. This varies based on the biochemical properties of the drug as well as the physiology of the individual taking that medication. In the body, a drug may be protein-bound or free. Only free drug can act at its pharmacologically active sites, e.g., receptors, cross into other fluid compartments, or be eliminated. Metabolism is the processing of the drug by the body into subsequent compounds. Excretion is the process by which the drug is eliminated from the body. The pharmacokinetic term half-life ($t1/_2$) refers to the time taken for half the initial dose of medicine administered to be eliminated from the body. After three to five half-lives the drug is considered undetectable and unable to exert a pharmacodynamic effect.

Keywords: body; drugs; pharmacokinetics

Introduction

Pharmacokinetics is derived from ancient Greek. Pharmakon means 'drug' and kinetikos means 'moving or putting in motion [1]. Pharmacokinetics, sometimes described as what the body does to a drug, refers to the movement of drug into, through and out of the body the time course of its absorption, bioavailability, distribution, metabolism, and excretion. Pharmacokinetics (PK) is the study of a drug and/ or its metabolite kinetics in the body. It refers to the temporary evolution of a drug and its metabolites in serum, plasma, or whole blood, tissue target and target organs over time. Another easy way to remember what pharmacokinetics means is to reference the definition of 'kinetics'. Kinetics essentially means movement, but by definition, it is the study of forces acting on mechanisms. The body is a very complex system and a drug undergoes many steps as it is being absorbed, distributed through the body, metabolised, and/ or excreted (ADME) [2]. Pharmacokinetics may be defined as the study of the dynamic movements of foreign chemicals (xenobiotics) during their passage through the body and as such encompass the kinetics of absorption, distribution, biotransformation/metabolism and excretion (ADME). It can simply be described as how the body handles xenobiotics [3-5].

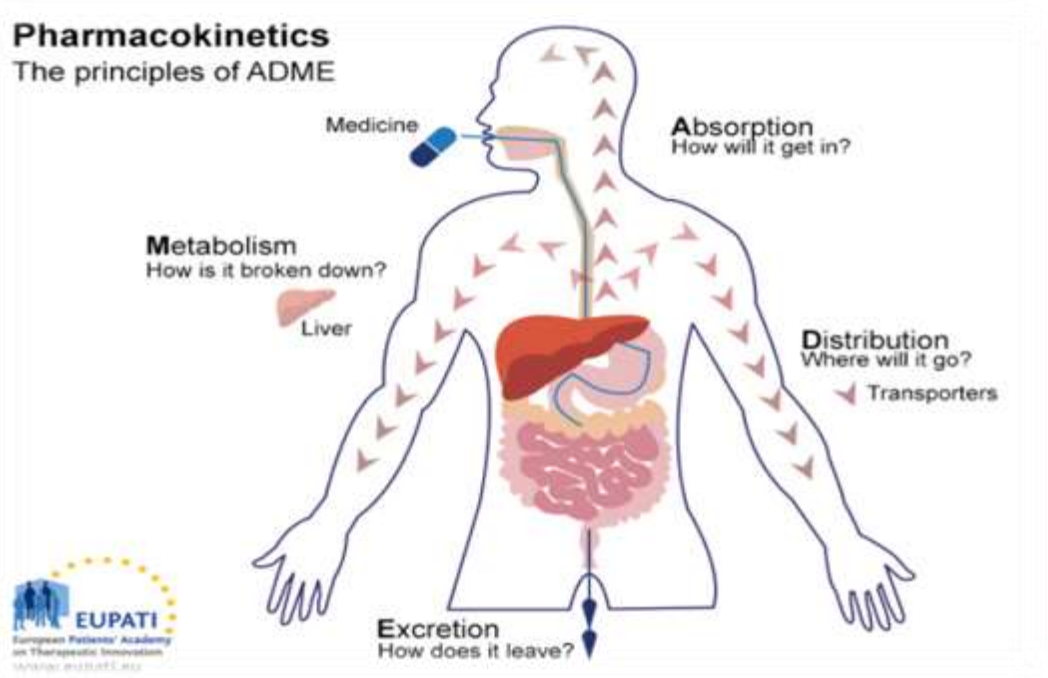

Figure 1: *Principles of ADME*

Pharmacokinetics of a drug depends on patient-related factors as well as on the drug's chemical properties. Some patient-related factors (eg, renal function, genetic makeup, sex, age) can be used to predict the pharmacokinetic parameters in populations. For example, the half-life of some drugs, especially those that require both metabolism and excretion, may be remarkably long in older people. In fact, physiologic changes with aging affect many aspects of pharmacokinetics. Other factors are related to individual physiology. The effects of some individual factors (eg, renal failure, obesity, hepatic failure, dehydration) can be reasonably predicted, but other factors are idiosyncratic and thus have unpredictable effects. Because of individual differences, drug administration must be based on each patient's needs traditionally, by empirically adjusting dosage until the therapeutic objective is met. This approach is frequently inadequate because it can delay optimal response or result in adverse effects [6]. Application of pharmacokinetic principles to individualize pharmacotherapy is termed therapeutic drug monitoring. The type of response of an individual to a particular drug depends on the inherent pharmacological properties of the drug at its site of action. However, the speed of onset, the intensity and the duration of the response usually depend on parameters such as: the rate and extent of uptake of the drug from its site of administration; the rate and extent of distribution of the drug to different tissues, including the site of action; the rate of elimination of the drug from the body [7, 8]. Pharmacokinetics influences the decided route of administration for a specific medication, the amount and frequency of each dose and its dosing intervals [9]. Potential drugs need appropriate pharmacokinetic properties to become safe, useable, effective therapeutics. In order to have a 'good' pharmacokinetic profile, a drug must: get into the bloodstream (A); move to the site of action (D); remain unchanged long enough to have a therapeutic effect and then be converted to safe metabolites (M); be adequately cleared (E) [10, 11]. Pharmacokinetics has been broadly divided into two categories of study: absorption and disposition. Disposition means the movement of medicines from site of application to different body fluids. Disposition is further subdivided into the study of distribution and elimination. The term elimination includes metabolism and excretion [12]

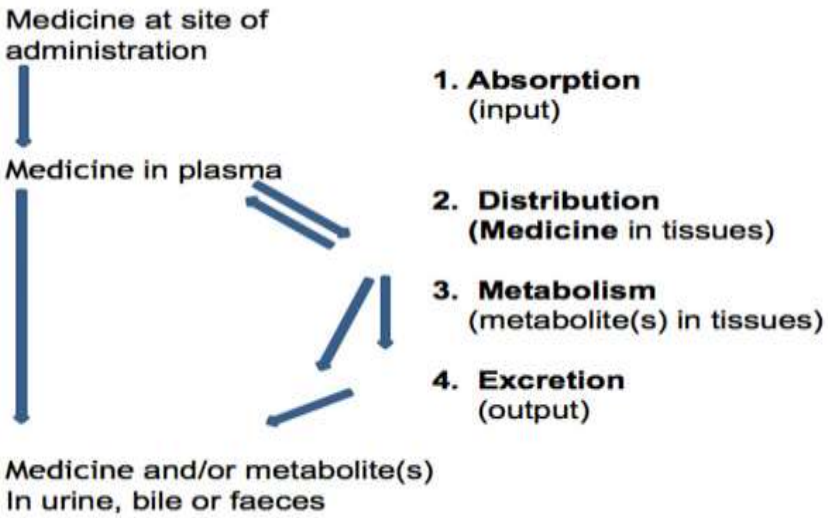

Figure 2: *Schematic representation of the absorption, distribution, metabolism and excretion of medicines*

Absorption

Absorption is the process that brings a drug from the administration, e.g., tablet, capsule, into the systemic circulation. Absorption affects the speed and concentration at which a drug may arrive at its desired location of effect, e.g., plasma. The process of absorption also often includes **liberation**, or the process by which the drug is released from its pharmaceutical dosage form [13]. Medicine-related factors include ionisation state, molecular weight, solubility and formulation. Small, nonionised, lipid-soluble medicines permeate plasma membranes most readily. Small molecules typically traverse membranes throughout this process, sometimes via passive transport, but often by way of proteins known as drug transporters. Drug transport can be a critical component of a drug's disposition in many steps of the pharmacokinetic journey, and preclinical studies should be conducted to provide information on how a drug interacts with various transporters as either substrates or inhibitors [14]. Absorption depends on the administration route and can either be enteral (by in the GI tract, such as by mouth, feeding tube, or rectal suppository) or parenteral (not in the GI tract, such as an injection or topical medication). Additional factors that can affect the amount of the drug absorbed include the drug's formulation (extended release versus immediate release), blood flow to the area of absorption, and GI motility (for enteral medications). The rate and extent of drug absorption depend on multiple factors, such as: route of administration; the formulation and chemical properties of a drug; drug-food interactions. X-rays decrease drug absorption by forming vasoconstriction while parasympathetic increases drug absorption by relaxing the smooth muscle of blood vessels. Gastric emptying time is slower in females' than males, mainly secondary to the effects of estrogen [15]. The administration (e.g., oral, intravenous, and inhalation) of a drug influences bioavailability, the fraction of the active form of a drug that enters the bloodstream and successfully reaches its target site. When a drug is given intravenously, absorption is not required, and bioavailability is 100% because the active form of the medicine is delivered immediately to the systemic circulation. However, orally administered medications have incomplete absorption and result in less drug delivery to the site of action. For example, many orally administered drugs are metabolized within the gut wall or the liver before reaching the systemic circulation. This is referred to as first-pass metabolism, which reduces drug absorption [16]. A drug's absorption may be impacted by many factors, including molecular weight, topological polar surface area, solubility, ionization, and other physicochemical properties. The first-pass effect (among other factors) after oral absorption will ultimately determine bioavailability [17]. The drugs absorbed in body fluids or skin, will diffuse through biological membrane barriers into the bloodstream. Diffusion can occur passively across the concentration gradient, which is the primary transport mechanism, or active transport, which requires energy, such as ATP; for drug transport across the blood brain barrier, neuronal membranes, renal tubular cells, and hepatocytes. It is important to note that only free, unionized drugs can cross cell membranes. There are several conditions that may influence the extent or rate of drug absorption, which include abnormal gastrointestinal motility, diseases of the stomach and well as of the small and large intestine, gastrointestinal infections, radiation, and interaction with other substances in the gastrointestinal tract, such as food [18]. Drugs must traverse a number of barriers to be absorbed, distributed, and eliminated. Major mechanisms are described in the following paragraphs. **Passive diffusion:** Passive diffusion is proportional to the concentration gradient of drug between two adjacent compartments, the thickness of the barrier, and the drug's ability to dissolve into the barrier separating the two compartments. These barriers are generally lipid membranes. Therefore the degree of ionization and the lipid solubility will affect passive drug transfer [19]. **Active transport:** Active transport is mediated by a very large family of transporters collectively referred to as ATP binding cassette transporters (or ABC transporters). These transporters rely on adenosine triphosphate (ATP) as a source of energy to transport drug molecules across biologic membranes. There are several important features of this mechanism, including saturability, structural selectivity, and ATP dependence [20]. **Saturability:** In contrast to passive diffusion, these carriers often exhibit a concentration beyond which no further increase in transport occurs.

Structural selectivity: These transporters exhibit a varying degree of structural selectivity for drugs and endogenous molecules. Structurally similar molecules will compete for binding at these transporters. This is an important mechanism of drug interaction. **ATP Dependence:** ATP dependence refers to the ability to move drugs against a concentration gradient. Examples of the ATP binding cassette group of transporters include the multidrug resistance transporters (MDR transporters) such as P-glycoprotein (Pgp, MDR1 or ABCB1). P-glycoprotein is an efflux transporter that transports drugs out of cell to the extracellular space. P-glycoprotein is found in a number of locations, including the gut and the blood-brain barrier. P-glycoprotein plays an important role in drug pharmacokinetics and in drug interactions. In the intestine, P-glycoprotein substrates that diffuse into intestinal epithelial cells are pumped back into the intestinal lumen, reducing their absorption. P-glycoprotein is also found in the endothelial cells of the blood brain barrier. Substances that diffuse into these cells and are substrates for P-glycoprotein can be transported back out into the blood, limiting their penetration into the brain. Drugs that inhibit P-glycoprotein increase the absorption of P-glycoprotein substrates. Drugs or disease conditions that induce P-glycoprotein decrease absorption of P-glycoprotein substrates. Intestinal p-gp levels do not consistently seem to vary by sex [21]. **Facilitated transport:** Facilitated transport is mediated by another large family of transporters collectively referred to as the human solute-linked carrier (SLC) family. This group of transporters is similar to the ABC transporters with the exception that they do not directly bind and hydrolyze ATP as a source of energy. Examples of this type of transporter include the organic ion transporter in the renal tubules that is responsible for secretion of some diuretics into the renal tubule, their site of action [22]. **Drug properties:** The general chemical properties of a drug can greatly influence its pharmacokinetics. For a drug to be absorbed and distributed to its site of action or its site of elimination, it must be liberated from its formulation, it must dissolve in aqueous solutions, and at the same time it must be able to cross several hydrophobic barriers (e.g., plasma membrane) [23]. **Drug formulations:** Solid formulations (e.g., tablets, capsules, suppositories) must disintegrate to release the drug. Disintegration of the dosage form may be compromised under certain conditions (e.g., dry mouth caused by aging, disease, or concurrent drug treatment slows dissolution of nitroglycerin tablets). On the other hand, drugs may be specifically formulated to allow disintegration only in certain sections of the gastrointestinal (GI) tract (e.g., enteric-coated tablets disintegrate in the small intestine), for the purpose of protecting the drug from destruction by gastric acid of the stomach (e.g., erythromycin) or protecting the stomach from an irritant drug (e.g., enteric-coated aspirin). Tablets and capsules may also be formulated to slowly release drugs (controlled-release, extended-release, or sustained-release formulations) and prolong their duration of action. Sustained-release formulations are particularly useful for drugs that have very short durations of action [24-26]. **Drug chemistry:** The physical and chemical properties of a drug will influence its ability to traverse biologic membranes and to be dissolved and transported in biologic fluids. Molecular size and shape: Smaller molecules are absorbed more readily. Drugs of similar structure may exhibit competition for such binding sites, which can affect their pharmacokinetics [27]. **State of ionization:** The nonionized form of drugs is more lipids permeable and therefore better able to diffuse across biologic barriers. The pK_a is a characteristic of the drug and reflects the pH at which the drug will be equally partitioned between the ionized and nonionized forms. The lipid-water partition coefficient is an index of lipid solubility. Drugs with higher lipid-water partition coefficients will cross biologic membranes more quickly [28]. **Effect of pH:** Most drugs are weak acids or bases and, as such, in solution show varying degrees of dissociation into their ionized and nonionized forms. The distribution between ionized and nonionized forms will be determined by the pK_a of the drug and the

pH of the solution in which the drug is dissolved [29]. Gastric fluids differ between men and women; gastric fluid is more acidic in males than females (pH=1.92 vs. pH=2.59), basal and maximal flow of gastric fluid and acid secretion is higher in men than women (reduced by 30% in pregnancy). Reduced pH results in decreased absorption of weak acids and increased absorption of weak bases. Under basic conditions, weak acids are ionized to a greater extent (because the basic environment will shift the reaction to the right). Under acidic conditions, weak acids are nonionized to a greater extent (because the acidic environment will shift the reaction to the left). The concepts of acidic and basic drugs and their relative ionization at different pH values can be used clinically. For example, acidification of the urine is used to increase the elimination of amphetamine, a basic drug with pK_a approximately 9.8. Rendering the urine acidic increases the amount of amphetamine in the ionized state, preventing its reabsorption from the urine into the bloodstream. Conversely, alkalinization of the urine is used to increase the excretion of acetylsalicylic acid (aspirin), an acidic drug. Increasing the pH of urine above the pK_a of acetylsalicylic acid increases the proportion of the drug in the ionized state by about 10,000 times. The ionized form of the drug is not able to be reabsorbed across the renal tubule into the bloodstream [29]. Variations in drug absorption; variations in drug distribution; differences in an individual's ability to metabolize and eliminate the drug (e.g., genetics); disease states (renal or hepatic insufficiency) or physiologic states (e.g., extremes of age, obesity) that alter drug absorption, distribution, or elimination; drug interactions. **Therapeutic monitoring** using drug concentration data is valuable when: (1) A good correlation exists between the pharmacologic response and plasma concentration. Over at least a limited concentration range, the intensity of pharmacologic effects should increase with plasma concentration. (2) Wide inter subject variation in plasma drug concentrations results from a given dose. (3) The drug has a narrow therapeutic index (i.e., the therapeutic concentration is close to the toxic concentration). (4) The drug's desired pharmacologic effects cannot be assessed readily by other simple means (e.g., blood pressure measurement for antihypertensives). The value of therapeutic drug monitoring is limited in situations in which: (1) There is no well-defined therapeutic plasma concentration range. (2) The formation of pharmacologically active metabolites of a drug complicates the application of plasma drug concentration data to clinical effect unless metabolite concentrations are also considered. (3) Toxic effects may occur at unexpectedly low drug concentrations as well as at high concentrations. (4) There are no significant consequences associated with too high or too low levels [30].

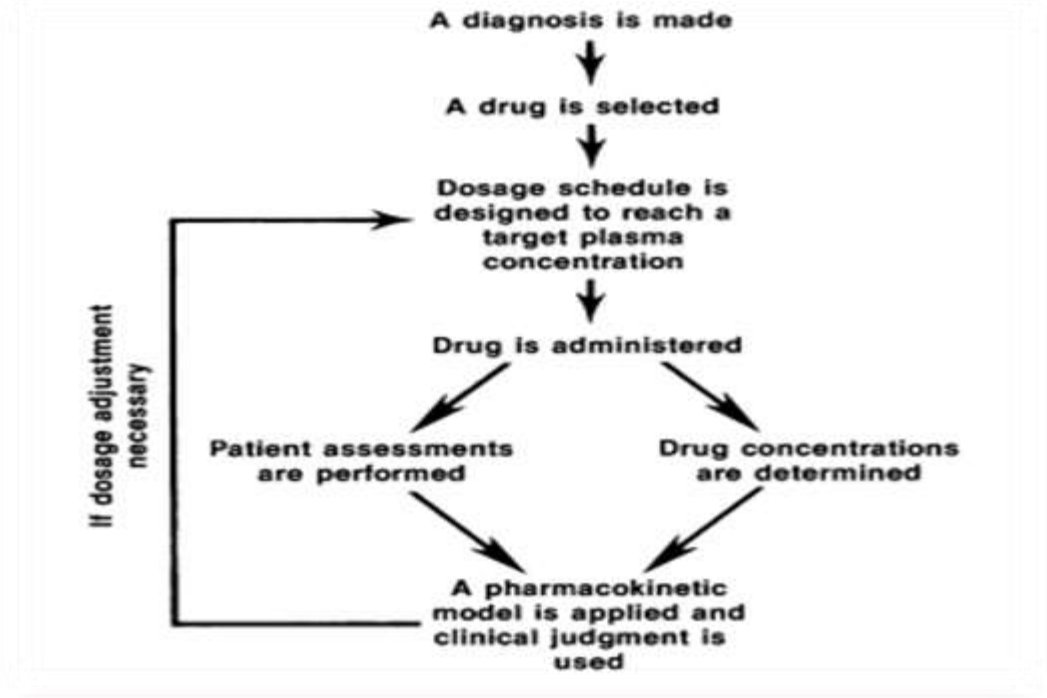

Figure 3: *Process for reaching dosage decisions with therapeutic drug monitoring.*

Bioavailability

Bioavailability is the fraction of the originally administered drug that arrives in systemic circulation and depends on the properties of the substance and the mode of administration. It can be a direct reflection of medication absorption. For example, when administering medication intravenously, 100% of the drug arrives in circulation virtually instantly, giving this method a bioavailability of 100% [30]. Drugs can be manufactured as a salt, crystal suspension, liposomes, liquid, oil, tablet, gel, and capsule or formulated for sustained or extended release. Factors influencing bioavailability include: route of drug administration, drug formulation, stability of the drug in the GI tract, characteristics of the drug for absorption and biotransformation, patient physiology and pathology, such as GI pH, GI motility, blood perfusion, bacterial flora, malabsorption states, kidney, liver and cardiac function and genetics. Drugs that are administered orally will undergo first-pass metabolism by the liver and lead to a decrease in drug bioavailability. Drugs administered intravenously or parenterally will bypass first-pass metabolism in the liver and have 100% bioavailability in systemic circulation. Of note, intermuscular injection of a drug does not guarantee a high percent of drug bioavailability because absorption of the drug is influenced by blood perfusion at the muscular site for injection [31]

Distribution

Distribution describes how a substance is spread throughout the body. This varies based on the biochemical properties of the drug as well as the physiology of the individual taking that medication. In its simplest sense, the distribution may be influenced by two main factors: diffusion and convection. These factors may be influenced by the polarity, size, or binding abilities of the drug, the fluid status of the patient (hydration and protein concentrations), or the body habitus of the individual. The goal of the distribution is to achieve what is known as the effective drug concentration. This is the concentration of the drug at its designed receptor site. To be effective, a medication must reach its designated compartmental destination, described by the volume of distribution, and not be protein-bound in order to be active. Women have lower body weights and lower BMI than men; women have a higher proportion of body fat than men; plasma volume is greater in men than women, although volume varies throughout

the menstrual cycle and during pregnancy; organ blood flow is greater in women than men. On average, total body water, extracellular water, intracellular water, total blood volume, plasma volume, and red blood cell volume are greater for men than women. Therefore, if an average male and an average female are exposed to the same dose of a water soluble drug, the greater total body water, plasma volume, extracellular water, and intracellular water will increase the volume of distribution thus decreasing drug concentration. As an example, the smaller volume of distribution for ethanol in women than men produces higher peak concentrations from the same dose [32]. Polar drugs are soluble in water and distribute to blood circulation and are primarily eliminated by the kidneys. Nonpolar drugs are lipid soluble. These drugs typically distribute to the central nervous system, tissue and fat. The drugs are primarily eliminated in feces and bile. This is dependent on blood flow, both to the area where the drug was administered and throughout the body as well as protein binding. If a drug binds to a protein it becomes stuck to it and cannot exert its effect on the body. It's an inverse proportion: the more a drug binds to protein; there is less of it available for distribution [33]. Once absorbed, the medicine may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids. A medicine's permeability is defined by the blood-brain barrier, blood-testes barrier and blood-placenta barrier. Many factors could influence this, such as blood flow, lipophilicity, molecular size, and how the drug interacts with the components of blood, like plasma proteins. For example, a drug like warfarin is highly protein-bound, which means only a small percentage of the drug is free in the bloodstream to exert its therapeutic effects. If a highly protein-bound drug is given in combination with warfarin, it could displace warfarin from the protein-binding site and increase the amount that enters the bloodstream. Additionally, there are anatomical barriers found in certain organs like the blood-brain barrier, preventing certain drugs from going into brain tissue. Drugs with certain characteristics, like high lipophilicity, small size, and molecular weight will be better able to cross the blood brain barrier. Most medicines are protein-bound to some extent; only an unbound medicine is free to carry out its pharmacological action(s). Depot Storage refers to lipophilic medicines that store in fat, calcium-binding drugs, etc. Medicine + plasma protein / Medicine-protein complex (inactive) / Protein + medicine (free to carry out pharmacological action/s) [34]

Protein Binding: In the body, a drug may be protein-bound or free. Only free drug can act at its pharmacologically active sites, e.g., receptors, cross into other fluid compartments, or be eliminated. In the clinical setting, the free concentration of a drug at receptor sites in plasma more closely correlates with effect than is the total concentration in plasma. The protein binding of the substance largely determines this. Any reduction in plasma protein binding increases the amount of drug available to act on receptors, possibly leading to greater effect or an increased possibility of toxicity. The principal proteins responsible for binding drugs of interest are albumin and alpha-acid glycoprotein [35]. Drugs that are highly protein-bound may be competitively displaced by another highly protein-bound drug. The pharmacologic effect of the displaced drug will increase as will renal clearance. In disease states characterized by hypoalbuminemia, the concentration of free drug will be higher in disease states characterized by the increase in acute phase proteins (A1AG), the free drug concentration will decrease. Therefore, the pharmacological activity of the drug is proportional to the free (unbound) concentration in blood. Endogenous substances (bilirubin, fatty acids) may displace a highly bound drug and in some patients with renal disease, without hypoalbuminemia, binding may decrease due to changes in protein charges of albumin. Albumin concentrations do not seem to consistently vary by sex, but endogenous estrogens decrease levels of AAG in the plasma, so women have lower concentrations of AAG than men. Exogenous estrogens increase levels of the serum-binding globulins (such as sex-hormone binding globulins, corticosteroid-binding globulin, and thyroxine-binding globulin) [36].

Metabolism or biotransformation

Metabolism is the processing of the drug by the body into subsequent compounds. This is often used to convert the drug into more water-soluble substances that will progress to renal clearance or, in the case of prodrug administration such as codeine; metabolism may be required to convert the drug into active metabolites [37]. Metabolism is the conversion of generally more lipophilic xenobiotic compounds to hydrophilic metabolites; abolishing drug pharmacological effects (to determine duration of action), converting prodrug to active parent drug; transforming active drug to more active metabolite (prolongs drug effects); transforming of drug to toxic metabolite; transforming drugs to chain of active drug (eg; diazepam) that can be eliminated from the body via excretion [10]. Metabolites may be more or less (prodrug) active than the parent medicine. The liver is the major source of cytochrome enzymes (P450 enzymes), though they may be present in the gastrointestinal tract, heart, lungs, brain and kidneys. **Phase I reactions (nonsynthetic):** Phase I reactions (nonsynthetic) involve minor structural modifications of the parent structure via oxidation, reduction or hydrolysis to produce smaller, more water-soluble metabolites. These are predominantly handled by the cytochrome P450 enzymes. The drug molecules can be metabolized by Phase I reactions, which alter chemical structure by oxidation, reduction, or hydrolysis to convert it into a more polar molecule for elimination. The cytochrome P-450 enzyme system plays important role in metabolism. Phase I reactions frequently provide a 'handle' for further modifications by subsequent Phase II reactions [38].

Phase II reactions (synthetic): Phase II reactions (synthetic) is involve the coupling of a water-soluble endogenous molecule such as glucuronic acid, sulfate or glutathione to a chemical (parent compound and/or Phase I metabolite) to facilitate excretion . Drugs can also be metabolized by enzymes for phase II reactions to conjugate with glutathione, glucuronide, sulfate, methyl-groups and acetyl-groups for conversion into water-soluble forms. The most common causes of medicine-to-medicine interactions are pharmacokinetics, particularly metabolic ones. These are known as cytochrome P450 interactions. A large number of clinically important interactions arise from inhibition or induction of substrates (medicines that are significantly metabolised by the given enzymes). **Inhibitors** are compounds that are generally capable of inhibiting the metabolism of the various substrates. As a result, administration of the inhibitor may lead to an increased plasma levels concentration of the substrate. For example, ciprofloxacin inhibits the CYP3A4 enzyme that metabolises clozapine, which may lead to a toxicity of clozapine by decreasing enzyme production and clozapine metabolism, ciprofloxacillin increase clozapine plasma concentration, then ciprofloxacillin ultimately cause clozapine toxicity [39]. **Inducers** of the specified P450 have the capacity to increase the activity of the designated enzyme and therefore reduce the plasma concentrations of the listed substrates. For example, carbamazepine induces the metabolism of cyclosporin via the CYP3A4 enzyme, leading to a reduction in plasma levels of cyclosporin and hence loss of efficacy by increasing enzyme production and metabolism of cyclosporin, carbamazepine decrease the plasma level concentration of cyclosporin, then ultimately cause cyclosporin failurity. Anti-cholesterol drugs known as statins and grapefruit juice are metabolized in using the same enzyme in the liver and will fight each other for it. That is why people taking statins should avoid taking them with grapefruit juice. Factors that affect drug metabolism: Genetics can impact whether someone metabolizes drugs more quickly or slowly. Age can impact liver function; the elderly have reduced liver function and may metabolize drugs more slowly, increasing risk of intolerability, and newborns or infants have immature liver function and may require special dosing considerations. Sex, female has unable to metabolize some drugs as male. Example; female is incapable to metabolize alcohol quickly as because of low amount of alcohol dehydrogenase enzyme or gastric levels of alcohol dehydrogenase are higher in males than females; intestinal CYP3A4 levels do not consistently vary by sex. Drug interactions can lead to decreased drug metabolism by enzyme inhibition or increased drug metabolism by enzyme induction. Having genetic variations in CYP2D6, the metabolic pathway for codeine can have significant clinical consequences. Usually, CYP2D6 poor metabolizers (PMs) have higher serum levels of active drugs. In codeine, PMs have higher serum levels of the inactive drug, which could result in inefficacy. Conversely, ultra-rapid metabolizers

(UMs) will transform codeine to morphine extremely quickly, resulting in toxic morphine levels.

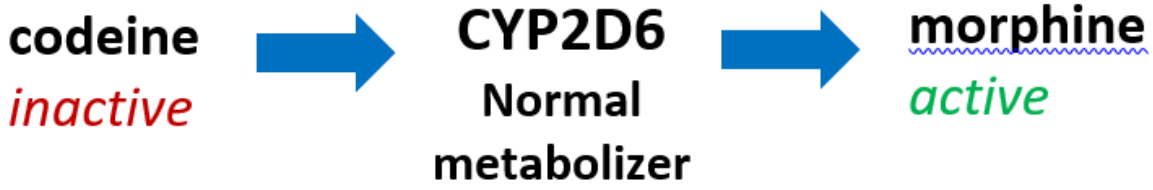

Figure 4: *Mechanism by which ultra-rapid metabolizers transform codeine (inactive) to morphine (active)*

Excretion

Excretion is the process by which the drug is eliminated from the body. The kidneys most commonly conduct excretion, but for certain drugs, it may be via the lungs, skin, or gastrointestinal tract. In the kidneys, drugs may be cleared by passive filtration in the glomerulus or secretion in the tubules, complicated by reabsorption in some compounds [39]. Excretion is the irreversible loss of a substance from the system. In most cases, all drug-related material, including parent drug and metabolites are eventually cleared from the body. It is important to characterize which routes of excretion are most important. Excretion commonly occurs by function of the kidney (urine) or liver (bile/feces), but the drug can also be excreted through sweat (for lipid soluble or lipophilic medicines), tears, or breath. Certain non-polar medicines, if it is lipid soluble excreted through sweat glands or skin without metabolism. Non-polar medicines excreted in unchanged way [10]. Excretion of drugs or chemicals from the body can occur through the lungs (for volatile/gaseous medicines), intestines, kidney and bile (for large molecular size medicines). However, renal excretion is a major pathway for the elimination of most water-soluble drugs or metabolites. Changes in renal function may have a profound effect on the clearance and apparent half-life of the parent compound or its active metabolite(s). For example, decreased renal function will cause serum drug concentrations to increase over time while the drug is being administered, which may lead to an increase in the pharmacological effects of the drug [40]. Many factors affect excretion, such as: direct renal dysfunction, which could prolong the half-life of certain drugs and necessitate dose adjustments. Age, which can contribute to differing rates of excretion and impact dosing of medications and pathologies that impact renal blood flow, such as congestive heart failure and liver disease can make drug excretion less efficient

The main parameters of pharmacokinetics described below as:

Half-Life

The pharmacokinetic term half-life ($t1/_2$) refers to the time taken for half the initial dose of medicine administered to be eliminated from the body. After three to five half-lives the drug is considered undetectable and unable to exert a pharmacodynamic effect [41]. That is: $t1/_2 = 0.693/ke$ (Where ke = first order elimination constant of the medicine). For example, a medicated dose with a half-life of 12 hours would have 25% of the medication left in the body after 24 hours. Many medications are classified in terms of their half-lives. For example, the benzodiazepines are classified in terms of: Ultra-short acting ($t1/_2$ < 6 hours): midazolam, triazolam; Short-acting ($t1/_2$ 6-12 hours): oxazepam, temazepam; Medium-acting ($t1/_2$ 12-24 hours): alprazolam, bromazepam, lorazepam; Long-acting ($t1/_2$ > 24 hours): clobazepam, clonazepam, diazepam, flunitrazepam, nitrazepam amount of drug in the body to be reduced by 50%. When drug is being administered as multiple doses or as a zero-order infusion, half-life also represents the time it takes for drug concentrations to reach one-half (or 50%) of the expected steady-state concentration. A useful approximate relationship among the clinically relevant half-life, clearance, and volume of distribution is given by $t1/_2$= volume/ CL *(0.693) [41].

Apparent volume of distribution

The pharmacokinetic measure used to indicate the pattern of distribution of a drug in plasma and in the different tissues, as well as the size of the compartment into which a drug would seem to have distributed in relation to its concentration in plasma, is known as the apparent volume of distribution (V_d). It is usually reported as liters per kilogram (L/kg) and is determined by measuring peak plasma drug concentrations after distribution has reached equilibrium for a drug administered IV. That concentration is compared with the IV dose that was given: V_d = dose/plasma drug concentration (PDC). For example, if 12 mg/kg of phenobarbital is given, and the resulting PDC after distribution has occurred is 20 mg/L, then the apparent volume to which phenobarbital is distributed (V_d) = (12 mg/kg/20 mg/L) = 0.6 L/kg [42]. For example, the mean digoxin V_d in dogs is 13 L/kg. For digoxin, the drug binds to cardiac tissue; however, this is known only because follow-up studies demonstrated as such. The V_d of a drug is usually constant over a wide dose range for a given species. However, a number of clinically significant factors can influence the V_d, including age (larger in neonates and pediatrics, smaller in geriatrics); functional status of the kidneys (decreased with dehydration), liver (increased with edema), and heart; fluid accumulations; concentration of plasma proteins (influencing unbound drug only); acid-base status (particularly if ion trapping causes the drug to accumulate in tissues); inflammatory processes or necrosis; and any other causes for alteration in the degree of plasma-protein binding distribute to plasma and well-perfused organs such as the heart, liver, kidney and brain. It will take minutes to hours for drugs to distribute to muscles and skin. It will take hours to days for drugs to distribute to fat stores. The limitations of Vd is that it may be based on total body water (~0.65 L/kg) and it doesn't estimate actual sites of distribution. In addition, volume of distribution may not account for individual differences in protein binding or tissue binding and it requires drug distribution to be complete. Volume of distribution = amount of drug /concentration. A large volume of distribution usually indicates that the drug distributes extensively into body tissues and fluids. Conversely, a small volume of distribution often indicates limited drug distribution. Volume of distribution indicates the extent of distribution but not the tissues or fluids into which the drug distributes. Two drugs can have the same volume of distribution, but one may distribute primarily into muscle tissues, whereas the other may concentrate in adipose tissues [34].

Drug clearance

Clearance is the volume of blood from which a drug is irreversibly eliminated, or cleared. Plasma is most commonly sampled; however, plasma clearance represents the sum clearances by all organs. If the drug is cleared by only a single organ, then plasma clearance is the clearance of that organ. Clearance is a volume and, as such, its units are volume/mass/time (eg, mL/kg/min). An alternative definition of clearance is the volume of plasma that would contain the amount of drug excreted per unit time; this definition demonstrates the link between volume of distribution (V_d) and clearance: if the elimination rate constant is known, it describes the fraction of the V_d cleared and,

together, they can be used to calculate clearance (CL) from the plasma drug concentration vs time curve: CL = $V_d \times k_e$/time (min). As such, like V_d, CL directly influences k_e, ie, rate at which drug is eliminated from the body: as CL increases, k_e becomes more steep. Clearance is independent of the V_d of a drug and thus the concentration of drug in the blood; no matter how much drug is in the blood, the same volume will be cleared per unit time. Division of the rate of elimination for each organ by a concentration of drug (e.g., systemic concentration) will yield the respective clearance by that organ. Other routes of elimination could include that in saliva or sweat, partition into the gut, and metabolism at sites other than the liver (e.g., nitroglycerin, which is metabolized in all tissues of the body) [33].

Elimination Rate Constant:

Among the most commonly cited pharmacokinetic parameters is the elimination half-life. It is derived from the elimination rate constant, k_e, which is the slope of the terminal, or elimination, component of the PDC vs time curve. A "hybrid" parameter, k_e is impacted by both CL and V_d. CL determines the decline in PDC; thus, the greater the volume of drug cleared the steeper the slope, or k_e. The impact of V_d on half-life reflects its effect on plasma drug concentration: a larger V_d means less drug is in the volume of blood cleared by the liver or kidneys. As such, the rate of elimination declines as V_d increases, resulting in an inverse relationship. The elimination half-life of a drug is the time that lapses as PDC declines by 50%. It is calculated from the slope of the line k_e: $t_{1/2} = 0.693/k_e$. The relationship between k_{el} and half-life reflects the fact that half-life becomes run of the slope (t_2-t_1) as C_1 declines by 50% (ie, $C_1/C_2 = 2$). The natural log of 2 = 0.693; because $t_{1/2}$ is the inverse of k_{el}, then $t_{1/2}$ is directly proportional to V_d (larger V_d results in a longer half-life) and inversely proportional to CL. Note that CL and V_d can be profoundly altered, yet $t_{1/2}$ may not change. For example, in an animal dehydrated because of renal dysfunction, CL may be decreased by 50%, doubling $t_{1/2}$. However, if the animal is markedly dehydrated, then V_d will decrease because of contraction of extracellular fluid volume. Because more drug is in each mL of blood cleared by the kidney, the same amount of drug may be eliminated, and as such k_e or $t_{1/2}$ may not change. The elimination half-life determines the time to steady-state (see below) and the time for a drug to be eliminated from the body once drug administration is discontinued. For practical purposes, most drugs is eliminated by 3–5 half-lives [33].

Kinetic models

Metabolism kinetics can occur at first-order, zero-order or nonlinear kinetics. First-order kinetics occurs when the amount of drug eliminated is dependent on the concentration of the compound and follows a logarithmic relationship over time. The clearance and Vd does not change with dose or concentration. Zero-order kinetics occurs when the rate of elimination is not dependent on the drug concentration. Examples of drugs that follow zero-order kinetics at high concentrations are: ethanol, phenytoin, salicylates. Capacity-limited or nonlinear kinetics occurs when the rate of elimination shifts from first-order to zero-order, based on saturation of elimination processes. Essentially any drug can become capacity-limited in an overdose situation [43].

Rates of reaction

To consider the processes of ADME the rates of these processes have to be considered; they can be characterised by two basic underlying concepts. The rate of a reaction or process is defined as the velocity at which it proceeds and can be described as either zero-order or first-order. **Zero-order reaction**; Consider the rate of elimination of drug "A" from the body. If the amount of the drug, A, is decreasing at a constant rate, then the rate of elimination of "A" can be described as: dA/dt=k; where k, the zero-order rate constant. The reaction proceeds at a constant rate and is independent of the concentration of "A" present in the body. An example is the elimination of alcohol. Drugs that show this type of elimination will show accumulation of plasma levels of the drug and hence nonlinear pharmacokinetics. **First-order reaction;** If the amount of drug "A" is decreasing at a rate that is proportional to "A", the amount of drug "A" remaining in the body, then the rate of elimination of drug "A" can be described as: dA/dt=KA; where k the first-order rate constant. The reaction proceeds at a rate that is dependent on the concentration of "A" present in the body. It is assumed that the processes of ADME follow first-order reactions and most drugs are eliminated in this manner. Most drugs used in clinical practice at therapeutic dosages will show first-order rate processes; that is, the rate of elimination of most drugs will be first-order. However, there are notable exceptions, for example phenytoin and high-dose salicylates. In essence, for drugs that show a first-order elimination process one can show that, as the amount of drug administered increases, the body is able to eliminate the drug accordingly and accumulation will not occur. If you double the dose you will double the plasma concentration. However, if you continue to increase the amount of drug administered then all drugs will change from showing a first-order process to a zero-order process, for example in an overdose situation [43].

Conclusion

Pharmacokinetics, sometimes described as what the body does to a drug, refers to the movement of drug into, through and out of the body the time course of its absorption, bioavailability, distribution, metabolism, and excretion. Liberation means the process of release of a drug from the pharmaceutical formulation. Pharmacokinetics of a drug depends on patient-related factors as well as on the drug's chemical properties. Absorption affects the speed and concentration at which a drug may arrive at its desired location of effect, e.g., plasma. The process of absorption also often includes liberation, or the process by which the drug is released from its pharmaceutical dosage form. Metabolism is the conversion of generally more lipophilic xenobiotic compounds to hydrophilic metabolites that can be eliminated from the body via excretion. The pharmacokinetic measure used to indicate the pattern of distribution of a drug in plasma and in the different tissues, as well as the size of the compartment into which a drug would seem to have distributed in relation to its concentration in plasma, is known as the apparent volume of distribution.

Abbreviations

ATP: Adenosine triphosphate; Cyp450: Cytochrome P450; L/ADME: Liberation/absorption, distribution, biotransformation/metabolism and excretion; CL: Clearance; K_e: elimination rate constant; PDC: Plasma drug concentration; Pgp: P-glycoprotein; PK: Pharmacokinetics; $T1/_2$: Half-life; Vd: Volume of distribution;

Acknowledgments

The author would be grateful to anonymous reviewers by the comments that increase the quality of this manuscript.

Data Sources: Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, Scopus database, Scielo and Cochrane database. Search terms included: about pharmacokinetics

Funding

None

Availability of data and materials

The datasets generated during the current study are available with correspondent author.

Competing interests

The author has no financial or proprietary interest in any of material discussed in this article.

References:

1. Ahammad F, Alam R, Mahmud R, Akhter S, Talukder EK, Tonmoy AM, Fahim S, Al-Ghamdi K, Samad A, Qadri I. (2021) Pharmacoinformatics and molecular dynamics

simulation-based phytochemical screening of neem plant (Azadiractha indica) against human cancer by targeting MCM7 protein. Brief. Bioinform.
2. Feghali M, Venkataramanan R, Caritis S. (2015) Pharmacokinetics of drugs in pregnancy. InSeminars in perinatology (Vol. 39, No. 7, pp. 512-519). WB Saunders.
3. Vrbanac J, Slauter R. (2017) ADME in drug discovery. InA Comprehensive Guide to Toxicology in Nonclinical Drug Development (pp. 39-67). Academic Press.
4. Shakil Ahmed Saghir, Rais Ahmad Ansari, (2018) in Reference Module in Biomedical Sciences,
5. Bisswanger H. (2017) Enzyme kinetics: principles and methods. John Wiley & Sons;
6. Shanbhag TV, Shenoy S, Nayak V. (2021). Pharmacology for Dentistry E-Book. Elsevier Health Sciences;
7. Holford N, Ma G, Metz D. (2020) TDM is dead. Long live TCI!. British Journal of Clinical Pharmacology.
8. Derek G. Waller Anthony P. Sampson , (2018) in Medical Pharmacology and Therapeutics (Fifth Edition),
9. Soldin OP, Mattison DR. (2009) Sex differences in pharmacokinetics and pharmacodynamics. Clinical pharmacokinetics. 48(3):143-157.
10. Loftsson, T. (2015) "Physicochemical Properties and Pharmacokinetics." Essential Pharmacokinetics, Pages 85-104.
11. Parkinson et al. (2018) "Biotransformation of Xenobiotics"Casarett & Doull's Toxicology, The Basic Science of Poisons Ninth Edition. Mcgraw-Hill Education Page 194.
12. McKenna MJ. (2020) The role of studies of absorption, metabolism, distribution and elimination in animal selection and extrapolation. InHuman Risk Assessment—The Role of Animal Selection and Extrapolation (pp. 113-128). CRC Press.
13. Slørdal L,Spigset O, (2005) [Basic pharmacokinetics--absorption]. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke.
14. Kalyane D, Raval N, Maheshwari R, Tambe V, Kalia K, Tekade RK. (2019) Employment of enhanced permeability and retention effect (EPR): Nanoparticle-based precision tools for targeting of therapeutic and diagnostic agent in cancer. Materials Science and Engineering: C. 1;98:1252-1276.
15. Abuhelwa AY, Williams DB, Upton RN, (2017) Foster DJ. Food, gastrointestinal pH, and models of oral drug absorption. European journal of pharmaceutics and biopharmaceutics. 1;112:234-248.
16. Yadav A, Mohite S. (2020) Recent advances in protein and peptide drug delivery. Res. J. Pharma. Dosage Forms and Tech. 2020; 12 (3): 205. 1;212.
17. Rossi Sebastiano M, Doak BC, Backlund M, Poongavanam V, Over B, Ermondi G, Caron G, Matsson P, Kihlberg J. Impact of dynamically exposed polarity on permeability and solubility of chameleonic drugs beyond the rule of 5. Journal of medicinal chemistry. 2018 Apr 2;61(9):4189-4202.
18. Luan X, Zhang LJ, Li XQ, Rahman K, Zhang H, Chen HZ, Zhang WD. (2020) Compound-based Chinese medicine formula: From discovery to compatibility mechanism. Journal of ethnopharmacology. 23;254:112687.
19. Min KA, Rosania GR. (2021) Measurement of Transcellular Transport Rates and Intracellular Drug Sequestration in the Presence of an Extracellular Concentration Gradient. InQuantitative Analysis of Cellular Drug Transport, Disposition, and Delivery (pp. 3-39). Humana, New York, NY.
20. Behl T, Kaur I, Sehgal A, Kumar A, Uddin MS, Bungau S. (2021) The Interplay of ABC Transporters in Aβ Translocation and Cholesterol Metabolism: Implicating Their Roles in Alzheimer's Disease. Molecular Neurobiology. 58(4):1564-1582.
21. Vasiliou V, Vasiliou K, Nebert DW. (2009) Human ATP-binding cassette (ABC) transporter family. Human genomics. 3(3):1-0.
22. Saunders NR, Habgood MD, Møllgård K, Dziegielewska KM. (2016) The biological significance of brain barrier mechanisms: help or hindrance in drug delivery to the central nervous system?. F1000Research. 5.
23. Shan N, Perry ML, Weyna DR, Zaworotko MJ. (2014) Impact of pharmaceutical cocrystals: the effects on drug pharmacokinetics. Expert opinion on drug metabolism & toxicology. 10(9):1255-1271.
24. Batchelor HK, Marriott JF. (2015) Formulations for children: problems and solutions. British journal of clinical pharmacology. 79(3):405-418.
25. Williams AC. (2018) Topical and transdermal drug delivery. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 5th ed. Edinburgh: Elsevier. 715-725.
26. Johnson AR, Forster SP, White D, Terife G, Lowinger M, Teller RS, (2021) Barrett SE. Drug eluting implants in pharmaceutical development and clinical practice. Expert Opinion on Drug Delivery. 10:1-7.
27. Pavlović N, Goločorbin-Kon S, Đanić M, Stanimirov B, Al-Salami H, Stankov K, Mikov M. Bile (2018) acids and their derivatives as potential modifiers of drug release and pharmacokinetic profiles. Frontiers in pharmacology. 8;9:1283.