PHARMACOKINETICS

Abstract

The study of a drug's absorption, distribution, metabolism, and excretion (ADME) in time is known as pharmacokinetics (PK). Pharmacokinetics, a branch of pharmacology, investigates the dynamic processes that govern the fate of drugs within the human body. This abstract provides a brief overview of essential pharmacokinetic principles and their implications for drug development and therapeutic optimization. The absorption phase involves the entry of drugs into the bloodstream, often influenced by factors such as drug formulation, route of administration, and physiological barriers. Distribution explores how drugs are transported to various tissues and organs, influenced by factors like blood flow, tissue binding, and drug lipophilicity. Metabolism, primarily occurring in the liver, transforms drugs into metabolites, affecting their activity and elimination. The elimination phase encompasses both metabolism and excretion, with renal and hepatic clearance playing key roles. Understanding these processes aids in predicting drug concentrations, optimizing dosages, and minimizing toxicity. These models help predict drug behavior, assess bioavailability, and guide dosing regimens in diverse patient populations. Furthermore, the application of pharmacokinetics extends to therapeutic drug monitoring, where individualized dosing is tailored based on patient-specific factors, ensuring optimal efficacy and safety. Pharmacokinetic models, including compartmental and non-compartmental approaches, facilitate quantitative analysis.

Keywords: Pharmacokinetics, Metabolites, Pharmacology, Drug Formulation.

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I. INTRODUCTION

The word, "drug" is derived from the Greek word "pharmacon" or "pharmakon," while the word "kinetics" means "in motion" or "positional change in regard to time."The term "pharmacokinetics" defines the movement of a medicine in vivo. When a patient takes the medication, various physiological actions take place. When a patient takes an oral dose type of medication by swallowing a tablet, it breaks down after it reaches the stomach and, in certain cases, the intestine (for example, tablet with enteric coating meant to dissolve only in the intestine). This leads to the drug to dissolve in the fluid of the stomach and the intestine. Drug molecules eventually absorb and enter the bloodstream, where they circulate throughout the body. The therapeutically effective drug level is then provided by the drug molecules, sometimes referred to as the blood minimum inhibitory concentration (MIC) or minimal effective concentration (MEC) of a medication (Fig. 1.1). The drug concentration in the blood is indicated by this level at or above which it is capable of producing systemic therapeutic action or an antibiotic inhibitory effect. The transport of drugs starts via transporting medications with an efficient concentration to the drug's target site. It produces its pharmacological effects, also known as "pharmacodynamic action," which refers to how the body eliminates a drug that has been taken. In the process of all these actions, the drug is also metabolized and removed from the body as a metabolite, drug, or both. The basic functional phenomena of a drug while it is moving in the body are absorption, distribution, metabolism, and elimination (ADME).All of these procedures require frequently changing the positions of drugs in our bodies. Pharmacokinetics is a term for a detailed mathematical explanation of this mechanism(ADME) in vivo of a drug.

II. PLASMA DRUG CONCENTRATION TIME PROFILE

The drug concentration in plasma and the number of drugs present in the biophase (site of action) are directly related. A plasma concentration time profile can be used to analyze two different parameters.

- Pharmacokinetics parameters
- Pharmacodynamic parameters

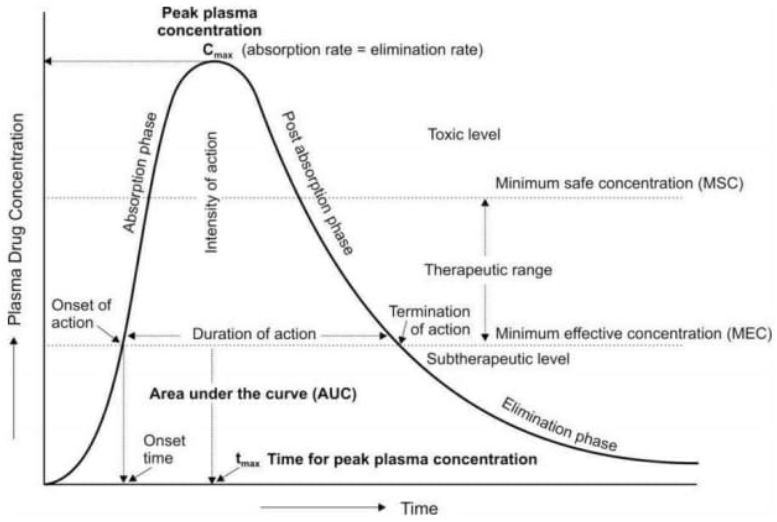

Figure 1: Pharmacokinetic and Pharmacodynamic Aspects of the Plasma

III. DEFINITIONS OF BASIC PHARMACOKINETIC PARAMETERS

It would be useful to maintain control of this concentration because a drug's effect is frequently correlated with its concentration at the site of action. However, because the sites of action are either typically difficult to access for direct observations or the treatments are widely disseminated throughout the body, direct measurement of drug concentration at the sites of action is not practical. When a specific medication exerts its therapeutic effects, a predictable relationship between plasma drug concentration and receptor site concentration is known as kinetics uniformity. Drug concentrations in most tissues are directly correlated with changes in plasma drug concentration. The definitions of common pharmacokinetic terminology are given in Table 1.

Table 1: Basics of Pharmacokinetic Parameters

Parameter.	**Definition.**
AUC: Area under the curve	The area under a drug concentration versus time graph.
Bioavailability. (BA)	The amount of the drug that is delivered that reaches in systemic circulation.
Clearance. (CL)	The rate at which blood purified when not using medications.
Half-life. ($t_{1/2}$)	The amount of time necessary for the drug's concentration to decrease by 50%. The cumulative result of all processes that lead to drug elimination is the half-life.
Time of Peak Concentration. (t_{max})	The period of time after administration that a medication needs to be absorbed before reaching its maximum concentration (Cmax). Tmax affects both the start of effect and the onset time.
Elimination. Rate. constant (Ke)	The speed at which a substance leaves the body in a certain amount of time. The half-life of a medication and the elimination rate constant are inversely related.
Extraction. Ratio.	An estimation of how much medication is eliminated from blood when it goes through an organ of elimination. The extraction ratio is affected by the blood flow rate, the free drug fraction, and the organ's inherent drug-elimination capacity.
First-Pass Effect	The procedure through which medications that have been ingested through the GI tract are metabolized in the liver. Drug bioavailability is decreased by first-pass metabolism because less of the drug reaches the systemic circulation. The term "first-pass effect" exclusively refers to drugs taken by mouth.
Plasma Protein. Binding	The process by which a drug binds to plasma proteins. Only unrestricted or free medications can often produce this pharmacologic action or be distributed, digested, or eliminated.
Steady State	A condition in which the rates of administration of medication and elimination are the same. Generally, a drug's steady state is attained four to five times during its half-life. It is preferable to monitor serum concentrations or assess the pharmacologic effects of a drug in a steady state. In order to determine how long it could take for a medicine to leave the body, steady state can also be used.

Volume of distribution (V_d)	It is not a physiologic volume; actually, it is a theoretical volume that links the supplied dose and plasma concentration. Drugs having a volume of distribution that is less than the intravascular volume tend to be hydrophilic, stay within the vascular compartment of the brain, and have a reduced affinity for binding plasma proteins. Drugs that are strongly plasma protein bound or lipophilic and diffuse to peripheral tissues typically have a very wide volume of distribution. They frequently have a distribution volume that is smaller and closer to the intravascular volume, without having a strong affinity for plasma protein binding. Drugs that are strongly plasma protein bound or lipophilic and diffuse to peripheral tissues have a relatively wide volume of distribution most of the time.

IV. PHARMACOKINETIC MODIFICATIONS IN A SPECIFICPOPULATION

Pharmacokinetics can be influenced by a range of physiological factors (such as age, ethnicity, or pregnancy) or pathological diseases (such as obesity, cardiac dysfunction, renal impairment, and hepatic impairment, and other factors).However, understanding how physiological and disease-related changes affect pharmacokinetics parameters might help pharmacists medication response can be predicted or optimized while toxicity is minimized. In individuals with changed PK, careful dose modification and regular monitoring of adverse events are required. In order to help pharmacists evaluate TDM results and provide patients with the best care possible overall, we will attempt to explain pharmacokinetic alterations in critically ill patients, juvenile patients, and geriatric patients in this chapter. Table 5 shows these changes.

1. **Changes in Pharmacokinetics in Critically ILL Patients:** The significant pathophysiological changes that take place in critically ill patients may affect how medicines are metabolized. The balance between the environment at the site of administration and the physical properties of the medicine might significantly alter or differ from the usual population during critical condition. Suboptimal drug concentration at the site of action will result from these anomalies, together with changes in transport, metabolism, and removal. Table 2 lists these modifications.

Table 2: Pharmacokinetic Changes in Critically Ill Patients

Parameter	Change	Effect	Example
Absorption	• Abnormalities in perfusion • Abdominal atrophy • Delayed gastric emptying • Increased gastric pH due to stress ulcer prophylaxis Interaction with enteral feeds	• Blood flow to important organs is diverted during shock, which results in decreased blood flow to GI systems. The systemic absorption of medicines from GI, intramuscular, and	• Significantly lower subcutaneously administered a medication known as concentration [1]. • In severely ill individuals, oral paracetamol's AUC and Tmax significantly decreased[2].

		subcutaneous tissues is decreased as a result of this deficiency. • Reduced Tmax, Cmax, and time until the pharmacological action starts to take effect. • AUC reduction for medicines with weak bases. • Reduction in AUC of selected medicines.	• Decreased the AUC of weak base drugs such dipyridamole, ketoconazole, intraconazole, and atazanavir[1-2]. • During gastrointestinal feedings, it has been found that phenytoin plasma concentrations decrease considerably[3].
Distribution	• An increase in interstitial space fluid volume and total body water (TBW) volume.	• If clearance remains unchanged, increasing Vd for hydrophilic medications like -lactam antibiotics may result in a decreased Cmax, a prolonged half-life, and a longer duration above the MIC. • Hydrophilic antibiotics that depend on concentration possible loss in effectiveness	• Oedema and the administration of a lot of fluids will increase the Vd of hydrophilic drugs[3-4]. • In severely sickness individuals, according to estimates, the Vd of gentamicin can reach 0.63L/kg.
	• Due to the systemic inflammatory response and other factors, Plasma albumin levels decrease when1-acid glycoprotein (AAG) level increase.	• An increase in the free fraction of substances like phenytoin that strongly bind to albumin. • Decrease the quantity of drugs like lidocaine and tricyclic antidepressants that are heavily bound to AAG in the free fraction.	• Phenytoin binding ratio and albumin levels are substantially associated[2,14]. • In a patient with hypoalbuminemia, a notable 99% increase in ceftriaxone clearance was observed associated with a 32% rise in Vd, which prevented the patient from reaching the pharmacodynamics target.
	• Alterations in plasma pH	• Change the the process hydrophilic	• Morphine-3- and 6-glucoronide entered

	• Septic shock • Acute neurotrauma accompanied With inflammation	medicines, such antibiotics, are distributed unbound in skeletal muscle and/or S/C tissues. • An increase in the concentration of free medicines in the CNS, possibly as a result of a decline in BBB efflux transporters (Pgp/MDR1 or MRPs).	the CSF more significantly in proportion to how much the pro-inflammatory cytokine IL-6 had risen.
Metabolism	• Hepatic dysfunction	• A decrease in liver function may cause medications that are processed in the liver to accumulate up.	
	• Shock-related decreased hepatic or splanchnic blood flow	• Decrease high extraction drug clearance from the liver.	• Metoprolol, midazolam, propranolol, and verapamil are examples of high extraction medications whose hepatic clearance is reduced during sepsis and septic shock because of changes in cardiac output that can increase or decrease hepatic blood flow.
Excretion	• Improved renal clearance (ARC)	• In comparison with the the initial state, the excretion of circulating metabolites, toxins, waste products, and medicines increases as a result of glomerular hyperfiltration.	• It was discovered that 63% of vancomycin-treated patients had vancomycin concentrations below 10 mg/L[8] . • Comparing levetiracetam clearance to that of healthy participants, it was greater.
	• Acute kidney damage (AKI)	• Levetiracetam clearance was higher when compared to that of participants in a healthy group.	• One of the active metabolites of allopurinol, oxypurinol, increases the risk of immune-mediated

			hypersensitivity. • When morphine's active metabolites accumulated, respiratory and CNS depression occurred[10].

2. **Pharmacokinetic Characteristics of Pediatrics:** Pediatric patients' developing bodies experience physiological and developmental changes that might affect when quickly and the amount of a medicine is absorbed. Throughout the earliest years of life, factors including water partitioning and plasma protein binding fluctuate regularly, altering how medications are distributed. Age-related variations in medication metabolism and elimination depend on the drug or substrate Table 3 includes a summary of these modifications.

Table 3: Pediatric Pharmacokinetic Features.

Parameter	Change	Effect	Example
Absorption	• Increase in gastric pH	• Lower the bioavailability of medicines for weak acidity. • The bioavailability of weak bases should be increased.	• While the gastric pH is typically neutral at birth, it decreases to 1-3 within the first 24 hours of life. By day ten of life, the pH has gradually shifted toward neutrality. The stomach's pH will resemble an adult by the age of three. Ampicillin, erythromycin, and amoxicillin are examples of drugs that are more efficiently absorbed when taken orally and are acid labile. Weak acid drugs like phenytoin, paracetamol, and phenobarbital will lack bioavailability.
	• Prolonged or delayed gastric emptying	• Delay the absorption of some medications	• In comparison to adults, the newborn era is characterized by a longer gastric emptying time. Amoxicillin, rifampicin, phenobarbital, digoxin, and sulphonamides have all been linked to delayed and ineffective absorption in newborns and small babies[1-5]
	• Alterations in the activity of the enzymes and transporters involved in	• The bioavailability of CYP3A4 substrates should be increased.	• Preterm newborns with immature CYP3A4 have greater oral midazolam bioavailability.

	intestinal drug metabolism.	• Reduced glutathione S-transferase (GST) substrate bioavailability	
	• Increased epidermis hydration	• An increase in the absorption of some medications	• Using steroids topically to newborns and babies may cause undesired systemic absorption and severe effects. This is because the epidermis is better hydrated, the subcutaneous layer is more perfused, and the body mass to total BSA ratio is higher in children than in adults.
Distribution	• Body water : fat ratio	• Increase the amount of hydrophilic medication distribution Reduce the amount of lipophilic drug distribution	• When an infant is born prematurely, 80–90% of their body weight is made up of water. Neonatals have an extracellular water level of about 45% compared to adults' 20%. These modifications will causing the Vd of hydrophilic to rise medications such phenobarbitone, propofol, vancomycin, gentamicin, and linezolid.
	• Reduce in protein binding	• An increase in the free fraction of medicines with strong protein binding	• An increase in the free fraction of medicines with strong protein binding
Metabolism	• A decrease in phase I and phase II hepatic metabolism	• Reduce hepatic clearance	• Age-related differences in CYP450 iso-enzyme development. The manner that medications that used this pathway are metabolized will be affected by these developmental changes. Theophylline metabolism in newborns is 50% slower than in adults due to the CYP1A2's delayedontogenesis[1]. • Morphine metabolism clearance by UGT2B7 is low in newborns and approaches adult levels between two and six months [6-7] .
Excretion	• Reduce in glomerular filtration rate • Decreased renal tubular	• Reduce renal clearance • Decreased renal clearance	• Infants frequently have decreased renal excretion of unmodified medications because of their undeveloped renal function.[7-8]. • However, there are sometimes

	secretion and absorption		exemptions for specific medications.
			• The capacity of the renal tubular secretion increases during the first several weeks of childhood and reaching adult levels at about seven months. In comparison to adults, the renal tubular secretion has a significant impact on how much digoxin is excreted in children and adolescents. • Amiodarone's suppression of renal tubular secretion may result in a greater rise in the serum levels of digoxin in children[9,10].

Table 4: Comparing Pediatric Population Isoenzyme Activity to Adult Population Using an Example [5].

Isoenzyme	Pediatrics population.	Activity Drug. class.	Examples.
CYP1A2.	Decrease till two years	Bronchodilator Antidepressant.	Theophylline Duloxetine.
CYP2C9.	decrease till one-two years	Antidepressant NSAIDs Anticoagulant	Warfarin. Phenytoin Ibuprofen, Diclofenac,Naproxen.
CYP2C19.	decrease till ten years	Benzodiazepine. PPIs Antidepressant	Citalopram, Diazepam Sertraline Pantoprazole
CYP2D6.	decrease till twelve years	Analgesic Antihistamine Antipsychotic. Antidepressant. Beta-blocker.	Codeine,.Tramadol Fluoxetine., Amitriptylline, Venlafaxine Diphenhydramine Risperidone Labetalol, Metoprolol
CYP3A4.	decrease till two years	Analgesic Antifungal Antiepileptic Antihistamine.Antiretroviral. Benzodiazepines.	Fentanyl Itraconazole, Carbamazepine Ketoconazole. Loratadine..Lopinavir, Indinavir,Indinavir, Ritonavir, .Saquinavir .Alprazolam, Midazolam
Mechanism of action A	until the last two years	-	-
Mechanism of action B	similarly, to an adult	-	-

N-Metyl transferases	similarly, to an adult	-	-
UGTs	Decrease until seven-ten years	Antiepileptic Analgesic Benzodiazepine	Morphine Clonazepam, Lamotrigine Lorazepam
UGTs	Decrease until 1-4 years	Anti-infective Antihypertensive.	Isoniazid Hydralazine.

3. **Pharmacokinetic Changes in Geriatrics:** Age-related physiological changes in geriatrics will impact different parts of the body and may disrupt pharmacokinetic procedures in various ways. Consequently, a drug's effects could be changed.

Table 5: Geriatric Pharmacokinetics Changes

Parameter	Change.	Effect.	Example.
Absorption	• Increased gastric. pH prolonged gastric. emptying • Reduce the flow of splanchnic blood. • Reduction in the absorption surface • Reduced transportation	• Reduced absorption slightly (rarely clinically significant) • Slightly enhance medication absorption after first-pass metabolism • Reduce the prodrug's bioavailability so that it can be activated in the liver.	• A higher concentration. of labetalol and propranolol. • Decreased. concentrations of ACE inhibitors such enalapril. and perindopril, which must be converted into active metabolites[10,11,12,]. • Levodopa is more readily absorbed when dopadecarboxylase in the stomach mucosa is reduced[15-17] .
Distribution	• Increase in body fat • Decrease in lean body mass • Decrease in body temperature generally	• Lipophilic drugs Vd and t1/2 should be increased. • Lower/smaller Vd with higher plasma concentrations of hydrophilic chemicals	• Decreased concentration and extended half-life of drugs that are lipophilic, such as lignocaine, thiopentone, and diazepam[16]. • Higher concentrations of theophylline, digoxin, lithium ethanol, and aminoglycosides, which are all water-soluble medicines[20-22].
	• Decreasing serum albumin levels	• An increase in the free proportion of highly protein-bound acidic medicines in plasma	• Increasing free-fraction of drugs that are strongly albumin-bound, including phenytoin and ceftriaxone [22-24] .
	• Increase in α1- acid glycoprotein	• Decrease free fraction of basic drugs	• Reduced free fraction of common medications like lignocaine and propranolol [23] .

	• Decrease in hepatic blood flow	• First-pass metabolism may not be as effective.	• Drugs with a high extraction ratio, such as glyceryl nitrate, lignocaine, pethidine, and propranolol, have a decreased clearance. [23].
	• A reduction in hepatic mass	• Some medications' phase I metabolism may be slightly hampered; phase II metabolism is recovered.	• Reduced liver phase I (oxidation and reduction) route drug metabolism clearance[24] .
	• Decrease in renal blood flow • Glomerular filtration rate decrease	• The ability of medications to be eliminated through the kidneys might be variablely impaired.	• Both oxidation and reduction reduced excretion of NSAIDS, digoxin, water-soluble adrenoceptor blockers, digoxin, antibiotics, and diuretics. If they accumulate even slightly more than intended by a drug with a narrow therapeutic index, significant side consequences are likely to occur. [25] .

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