**PHARMACOKINETICS**

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**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 swallows a pill as an oral dosage form of medication, it breaks down after it reaches the stomach and, in certain cases, the intestine (for example, an enteric-coated tablet 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 drug molecules then provide the therapeutically effective drug level, also known as the minimum effective concentration (MEC) or minimum inhibitory concentration (MIC) of a drug in the blood (Fig. 1.1). This level refers to the drug concentration in the blood 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) of a drug in vivo.

**PLASMA DRUG CONCENTRATION TIME PROFILE**

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

1) *Pharmacokinetics parameters*

2) *Pharmacodynamic parameters*

 (Fig.1.1) Pharmacokinetic and pharmacodynamic aspects of the plasma

**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. Direct measurement of drug concentration at the sites of action, however, is not possible due to the sites of action are either generally difficult to access for direct observations or the medications are broadly circulated around the body. 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. Table 1 provides common terms and definitions related to pharmacokinetic.

Table 1: Definitions of basic pharmacokinetic parameters

|  |  |
| --- | --- |
| **Parameter** | **Definition** |
| Area under the curve (AUC) | A drug concentration versus time graph's area under |
| Bioavailability (BA) | The amount of the drug that is delivered that reaches the systemic circulation |
| Clearance (CL) | The volume of without drugs blood cleared per unit of time. |
| Half-life (t1/2) | 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 (tmax) | 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 rate at which the drug exits the body per unit of time. The connection between the elimination rate constant and drug half-life is inverse. |
| 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 method by which a medication attaches to plasma proteins. Usually, only free or uncontrolled drugs are capable of carrying out this pharmacologic effect or of being dispersed, metabolized, or excreted. |
| Steady State | a state where the rate of drug administration and drug elimination are identical. 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 (Vd) | This is a theoretical volume that connects the plasma concentration to the administered dose; it is not a physiologic volume. Drugs having a volume of distribution that is less than the intravascular volume tend to be hydrophilic, stay in the central (vascular) compartment, 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 tend to have a reduced volume of distribution, with a value that is 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 typically have a very wide volume of distribution. |

**PHARMACOKINETIC CHANGES IN SPECIFIC POPULATION**

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 predict/optimize drug response while reducing its toxicity. 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.

**a) PHARMACOKINETIC CHANGES 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 | * Perfusion abnormalities
* Intestinal 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 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.
 | * Significantly lower subcutaneously administered a medication known as concentration [1].
* In severely ill individuals, oral paracetamol's AUC and Tmax significantly decreased[2].
* 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, the Vd of gentamicin has been estimated to be as high as 0.63L/kg.
 |
|  | Due to the systemic inflammatory response and other factors, there is a decrease in plasma albumin and an increase in 1-acid glycoprotein (AAG). | * Increase in free fraction of drugs that are highly bind to albumin such as phenytoin.
* Reduce 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
* Septic shock
* Acute neurotrauma accompanied with inflammation
 | * Change the the process hydrophilic medicines, such antibiotics, are distributed unbound in skeletal muscle and/or S/C tissues.
* An increased accumulation of free drugs in the CNS, potentially as a result of BBB efflux transporters (Pgp/MDR1 or MRPs) being decreased.
 | * Morphine-3- and 6-glucoronide entered 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 | * Augmented renal clearance (ARC)
 | * As a result of glomerular hyperfiltration, there is an increase in the excretion of circulating metabolites, toxins, waste products, and drugs relative to baseline.
 | * 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 injury (AKI)
 | * Levetiracetam clearance was higher when compared to that of participants in a healthy group.
 | * Oxypurinol, one of allopurinol's active metabolites, raises the possibility of immune-mediated hypersensitivity
* The accumulation of morphine's active metabolites resulted in respiratory and CNS depression[10] .
 |

**b) 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. The age-related differences in drug metabolism and elimination depend on the drug or substrate Table 3 includes a summary of these modifications.

Table 3: Pharmacokinetic characteristics of paediatrics.

|  |  |  |  |
| --- | --- | --- | --- |
| 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 10 of life, the pH has progressively become neutral. By the age of three, the gastric pH will resemble that of an adult. Orally administered acid labile medications including ampicillin, erythromycin, and amoxicillin are more effectively absorbed. The bioavailability of weak acid medications such phenytoin, paracetamol, and phenobarbital will be minimal.
 |
|  | * 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 intestinal drug metabolism.
 | * The bioavailability of CYP3A4 substrates should be increased.
* Reduced glutathione S-transferase (GST) substrate bioavailability
 | * Immature CYP3A4 in preterm infants has leads to higher bioavailability of oral midazolam.
 |
|  | * 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 ratio of total BSA to body mass 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 lead to an increase in the Vd of hydrophilic 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 | * Reduce in phase I and phase II liver 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 delayed ontogenesis[1] .
* Metabolism clearance of morphine by UGT2B7 is low in neonates and reaches adult levels between 2 and 6 months[6-7] .
 |
| Excretion | * Reduce in glomerular filtration rate
 | * Reduce renal clearance
 | * Due to their immature renal function, infants often have reduced renal excretion of unaltered drugs[7-8].
* However, there are sometimes exemptions for specific medications.
 |
|  | * Decreased renal tubular secretion and absorption
 | * Decreased renal clearance
 | * 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: Isoenzyme activity in pediatric population compared to adult with example [5]

|  |  |  |  |
| --- | --- | --- | --- |
| **Isoenzyme**  | **Paediatrics population** | **Activity Drug class** | **Examples** |
| CYP1A2  | Decrease till 2 years | Bronchodilator Antidepressant  | Theophylline Duloxetine |
| CYP2C9 | decrease till 1-2years | Antidepressant NSAIDs Anticoagulant | Warfarin Phenytoin Ibuprofen, Diclofenac, Naproxen |
| CYP2C19 | decrease till 10 years | Benzodiazepine PPIs Antidepressant | Citalopram, Diazepam Sertraline Pantoprazole |
| CYP2D6 | decrease till 12 years | Analgesic Antihistamine Antipsychotic AntidepressantBeta-blocker | Codeine, Tramadol Fluoxetine, Amitriptyline, Venlafaxine Diphenhydramine Risperidone Labetalol, Metoprolol |
| CYP3A4 | decrease till 2 years | Analgesic Antifungal Antiepileptic Antihistamine Antiretroviral Benzodiazepines | Fentanyl Itraconazole, Carbamazepine Ketoconazole Loratadine Lopinavir, Indinavir, Indinavir, Ritonavir, Saquinavir Alprazolam, Midazolam |
| MAO A | until the last 2 years | - | - |
| MAO B | similarly, to an adult | - | - |
| N-Methyltransferases | similarly, to an adult | - | - |
| UGTs | Decrease until 7-10 years | Antiepileptic Analgesic Benzodiazepine | Morphine Clonazepam, Lamotrigine Lorazepam |
| UGTs | Decrease until 1-4 years | Anti-infective Antihypertensive  | Isoniazid Hydralazine  |

**c) PHARMACOKINETICS CHANGES IN GERIATRICS**

In geriatrics, age-related physiological changes will affect body systems and can alter pharmacokinetic processes in different ways. Consequently, a drug's effects could be changed.

Table 5: Pharmacokinetics changes in geriatrics

|  |  |  |  |
| --- | --- | --- | --- |
| 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 total body wate
 | * Lipophilic drugs Vd and t1/2 should be increased.
* Decreased/smaller Vd with increased plasma levels of hydrophilic substances
 | * 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].
 |
|  | Decrease in serum albumin | Increase free fraction in plasma of highly protein-bound acidic drugs | Increased free-fraction of highly albumin bound drug such as phenytoin and ceftriaxone [22-24] . |
|  | Increase in α1- acid glycoprotein | Decrease free fraction of basic drugs | Decreased free fraction of basic drugs such as lignocaine and propranolol [23] . |
|  | Decrease in hepatic blood flow | First-pass metabolism can be less effective | Reduced clearance of drugs with a high extraction ratio such as glyceryl nitrate, lignocaine, pethidine, and propranolol [23]. |
|  | Decrease in hepatic mass | Phase I metabolism of some drugs might be slightly impaired; phase II metabolism is restored | Reduced clearance of drugs metabolized by phase I pathway in the liver (oxidation and reduction) [24] . |
|  | * Decrease in renal blood flow

Decrease in glomerular filtration rate | Renal elimination of drugs can be impaired to a variable extent | Reduced clearance of water-soluble antibiotics, diuretics, digoxin, water-soluble adrenoceptor blockers, lithium, and NSAIDS. Drug with narrow therapeutic index is likely to cause serious adverse events if they accumulate only marginally more than intended [25] . |

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