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• *Review* •

Pharmacokinetic Characteristics of Drugs and Their Effects on Therapeutic Efficacy and Safety

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Abstract: The absorption, distribution, metabolism, and excretion of drugs in the body collectively shape the exposure-time curve, which largely determines the intensity of therapeutic response, onset rate, duration, and spectrum of adverse reactions. With the advancement of new drug development and the concept of personalized treatment, the issue of significant differences in exposure at the same dose regimen, as well as inconsistent efficacy and toxicity profiles, has become increasingly prominent. Pharmacokinetic (PK) characteristics thus serve as the critical link connecting "dose-exposure-therapeutic effect/safety." This article systematically reviews the core concepts of PK from four dimensions—absorption, distribution, metabolism, and excretion—explains their impact pathways on onset and duration, targeting and therapeutic window, as well as acute and chronic toxicity risks. Based on this, it discusses clinical optimization strategies for drug use based on pharmacokinetic characteristics, providing insights for exposure control, risk identification, and individualized dosing.

Keywords: Drug exposure; Therapeutic window; Individualized dosing

Modern pharmacotherapy continues to advance in expanding indications and refining target mechanisms, yet phenomena such as "same dose, different responses" and "coexistence of insufficient efficacy and toxicity" remain prevalent in clinical practice, indicating that reliance solely on empirical dosing is insufficient to fully account for interindividual variability. Pharmacokinetics (PK) focuses on concentration-time profiles to characterize the absorption, distribution, metabolism, and excretion of drugs in vivo, providing a foundational framework for understanding the quantitative relationships between dose, exposure, and effect. Clinical pharmacological studies have demonstrated that exposure levels and their temporal patterns are closely associated with therapeutic intensity, toxicity thresholds, and therapeutic window width, particularly in narrow therapeutic window drugs and populations with multi-organ involvement [1]. Against this backdrop, a systematic review of PK characteristics and their impact on efficacy and safety can enhance the scientific rigor of dose

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design, facilitate the transition from "empirical dosing" to "evidence-and model-driven dosing," and provide theoretical support for subsequent exposure-based clinical strategies.

1 Pharmacokinetic Characteristics

1.1 Absorption Characteristics: Absorption Rate and Absorption Degree

The process of drug entering systemic circulation from the site of administration is governed by multiple factors, including formulation characteristics, route of administration, local blood flow, membrane permeability, and transporter activity. The absorption rate primarily influences the time to peak and peak concentration, thereby determining the speed of onset and the intensity of early effects. The extent of absorption determines the total amount entering systemic circulation and is closely related to the area under the curve (AUC). For oral formulations, dissolution behavior, gastric emptying time, first-pass effect, and intestinal mucosal metabolism collectively shape relative bioavailability. Sustained-release and controlled-release technologies can reshape the rate process without altering the total absorption, resulting in reduced peak-to-valley differences and more stable exposure. Variations in gastrointestinal function, concomitant medications, and dietary habits among individuals can lead to significant absorption variability, making "absorption rate and extent at the same dose" the starting point for explaining individual exposure differences.

1.2 Distribution characteristics: Distribution volume and tissue binding rate

The process of drug diffusion from blood to interstitial spaces and intracellular environments essentially reflects the combined effects of distribution volume and tissue binding rate. A larger apparent distribution volume corresponds to a higher total body concentration per unit blood drug concentration, indicating greater distribution of the drug in tissues or cells, often accompanied by enhanced lipophilicity, increased tissue affinity, or high tissue binding. Tissue binding rate determines the allocation ratio of the drug between target and non-target organs. High selective distribution in diseased tissues often facilitates increased local effective concentrations and reduced systemic exposure. The level of plasma protein binding rate also affects the proportion of free drug, thereby influencing pharmacological effects and clearance pathways. Population pharmacokinetic studies demonstrate that different disease states and physiological characteristics (e.g., changes in body composition, fluctuations in plasma protein levels) significantly alter the effective distribution volume, thereby interfering with the stability of the concentration-effect relationship [2].

1.3 Metabolic Characteristics: Metabolic Pathways and Metabolic Rates

Metabolic processes convert the parent drug into more polar and excretable metabolites through a series of enzymatic reactions. Some metabolites retain activity and may even exhibit independent pharmacological effects. The metabolic pathway involves reactions such as oxidation, reduction, hydrolysis, and conjugation, with the liver serving as the central site, while tissues like the intestines and kidneys also participate. The metabolic rate is determined by factors such as enzyme activity, hepatic blood flow, protein binding, and genetic polymorphisms, which directly influence the half-life, clearance rate, and the time required to establish steady-state concentrations. Drugs with high metabolic clearance exhibit significant

exposure fluctuations due to changes in hepatic blood flow and enzyme induction/inhibition, whereas drugs with low extraction are more susceptible to variations in protein binding and enzyme activity. The diversity and redundancy of metabolic pathways not only enhance the body's ability to process exogenous compounds but also create conditions for drug-drug interactions and the formation of toxic metabolites, making metabolic characteristics one of the key links between therapeutic efficacy and safety.

1.4 Excretory Characteristics: Excretion Pathways and Efficiency

The excretion process encompasses renal filtration and secretion, bile excretion, fecal elimination, as well as other pathways such as pulmonary and sweat excretion, whose combined efficiency constitutes the total drug clearance. Renal excretion depends on glomerular filtration rate, renal tubular secretion, and reabsorption function, while hepatobiliary excretion is closely related to transporter expression and bile flow. Higher excretion efficiency results in shorter drug residence time in the body, making steady-state concentrations more susceptible to adjustments in dosing frequency and dose. Conversely, reduced excretion prolongs the half-life and increases the risk of accumulation, particularly in populations with impaired renal or hepatic function. Some drugs or metabolites undergo repeated absorption via enterohepatic circulation, leading to an elongated tail in the exposure curve and a deviation between the duration of effective exposure and the static half-life. Variations in excretion pathways and efficiency not only reshape the exposure-time profile but also directly influence dose adjustment strategies and monitoring priorities for specific populations, representing a critical terminal step in individualized drug administration design that cannot be overlooked.

2 Mechanisms of Drug Metabolism Kinetics Characteristics on Drug Efficacy

2.1 Absorption characteristics dominate the onset and intensity of therapeutic effects

Clinically observed phenomena such as "slow onset of action" or "suboptimal early efficacy" are frequently associated with either low absorption rates or delayed absorption. Conversely, rapid absorption leads to a short-lived peak concentration, resulting in swift pharmacological responses. The extent of absorption directly correlates with total drug exposure. When bioavailability decreases, even with unchanged nominal dosing, the actual amount of drug entering the body becomes insufficient to sustain concentrations above the minimum effective level for prolonged periods, manifesting as diminished efficacy during treatment mid-course. The absorption patterns shaped by different formulation designs exhibit varying compatibility between acute conditions and chronic therapies: immediate-release formulations are suitable for scenarios requiring rapid onset, whereas sustained-release formulations are better suited for maintaining relatively stable exposure levels.

2.2 Distribution characteristics determine therapeutic targeting

The efficacy of a drug depends on the effective concentration at the target tissue, not merely the total plasma concentration. Although an increased volume of distribution reflects broad tissue penetration, it does not necessarily equate to enhanced targeting; the key lies in the drug's affinity for the lesioned tissue and its transmembrane transport

capability. Highly lipophilic compounds that readily penetrate the blood-brain barrier are more likely to accumulate in the central nervous system, ensuring adequate exposure to central targets, whereas molecules with higher hydrophilicity are often confined to vascular and interstitial spaces, making them suitable for action in intravascular or glomerular sites. When the plasma protein binding ratio changes, the proportion of free drug also varies accordingly. The free fraction is the "effector entity" that directly interacts with receptors, and its distribution pattern often differs from the total concentration. Once the distribution characteristics deviate from expectations, systemic exposure may appear adequate but fail to achieve sufficient concentrations in target organs, resulting in a mismatch where "lab metrics are favorable but clinical improvement is limited" [3].

2.3 Duration of Therapeutic Efficacy Regulated by Metabolic Characteristics

Metabolic rate is the core variable determining half-life and the plateau height of steady-state concentration, thereby shaping the duration of therapeutic efficacy and dosing intervals. When metabolism is rapid, drug concentrations decline rapidly, and excessively long dosing intervals may cause trough concentrations to fall outside the therapeutic window, leading to discontinuous efficacy or "rebound" phenomena. Conversely, when metabolism is slow, lower dosing frequencies can maintain stable exposure, while overly frequent dosing may result in accumulation. The extent of involvement of different enzymatic pathways determines the level of metabolic redundancy. When the primary metabolic pathway is inhibited or saturated, alternative pathways may be passively amplified, altering the pharmacodynamic profile and the temporal pattern of therapeutic effects. For drugs with well-defined exposure-response relationships, pharmacokinetic/pharmacodynamic models can be used to evaluate exposure distribution across populations with different metabolic phenotypes, enabling more refined dose-level stratification. This approach ensures that the duration of therapeutic efficacy aligns with disease rhythms while avoiding unnecessary peak-valley fluctuations [4].

2.4 Excretion characteristics ensure therapeutic stability

During maintenance therapy, therapeutic stability relies on minor fluctuations of steady-state concentrations within the target range, with excretion characteristics being one of the decisive factors in maintaining steady-state levels. When excretion is moderate, slight adjustments to the dosing regimen and dosing interval can fine-tune steady-state levels within a reasonable range, ensuring both efficacy and tolerability remain under control. Excessive excretion requires increasing the daily dose or shortening the dosing interval to avoid insufficient trough concentrations, whereas slowed excretion may lead to a gradual elevation of the steady-state plateau even without altering the dosing regimen. For drugs excreted via bile with enterohepatic circulation, any disruption of the excretion-reabsorption balance due to intestinal flora, bile secretion, or intestinal diseases can result in unpredictable tailing of the exposure curve.

3 Impact of Pharmacokinetic Characteristics on Drug Safety

3.1 Absorption abnormalities leading to acute toxicity risk

When the absorption process deviates from the preset pattern, safety risks often first manifest

through acute adverse reactions. Rapid absorption leading to peak concentrations may exceed the toxic threshold within a short period, inducing acute events such as arrhythmias, central nervous system depression, hypotension, or anaphylactoid reactions, which are particularly evident during rapid intravenous infusion. Conversely, impaired absorption resulting in prolonged local mucosal exposure may also cause irritation or injury at the administration site. Gastrointestinal dysfunction, nonstandard administration techniques, and interactions with food or other drugs can alter the dissolution environment and permeability conditions, leading to clinical absorption profiles that exhibit "broad and narrow peaks" or "multi-peak" patterns. For narrow therapeutic window drugs, even minor fluctuations during the absorption phase may be sufficient to exceed the safety threshold, necessitating more refined strategies in dosage control, timing of administration, and management of absorption interactions.

3.2 Distribution abnormalities leading to off-target organ toxicity

When drug distribution in the body shifts toward non-target organs, toxic events may first manifest at sites "not directly related to the intended indication." Excessive lipophilicity or abnormal tissue affinity enhancement predisposes drugs to accumulate in adipose tissue, myocardium, liver, or the central nervous system, resulting in significantly higher local concentrations than the plasma average. Even when overall exposure remains within traditional safety limits, local tissues may experience subthreshold exposure. A sudden increase in the proportion of free drug occurs when plasma protein levels decline or protein binding sites are competitively occupied by other drugs, leading to enhanced free distribution at the same total concentration and amplifying micro-level effects such as cytotoxicity and mitochondrial damage. Population pharmacokinetic studies suggest that alterations in organ perfusion status, barrier integrity, and transporter expression profiles can rewrite distribution patterns, transforming non-target organ toxicity from "isolated cases" into an anticipated risk in specific populations [5].

3.3 Metabolic abnormalities induce accumulation of toxic products

Metabolic pathways serve as both the routes for drug inactivation and potential sources of toxic metabolite generation. Certain drugs are converted into non-toxic or low-toxic metabolites through primary metabolic pathways at conventional doses. However, when enzyme activity is inhibited, substrate competition intensifies, or the dose is excessively high, alternative metabolic pathways may be passively amplified, producing highly reactive free radicals or electrophilic intermediates that can induce hepatotoxicity, hematopoietic suppression, or immune-mediated adverse reactions. Genetic polymorphisms also alter metabolic profiles, with patients exhibiting high-activity metabolites being more prone to generating toxic metabolites, while those with low-activity metabolites experience elevated exposure due to slower clearance of the parent drug.

3.4 Risk of chronic toxicity due to excretory abnormalities

When excretory function declines, the clearance rate of drugs and their metabolites in the body significantly decreases, leading to an upward drift in steady-state concentrations. Prolonged exposure levels exceed the original safety threshold, thereby increasing the risk of chronic toxicity. Renal impairment substantially prolongs the half-life

of drugs excreted via the kidneys, often resulting in the cumulative manifestation of neurotoxicity, ototoxicity, or hematologic toxicity after repeated administration. Impaired bile excretion causes drug accumulation in hepatocytes and the biliary system, potentially leading to complications such as cholestasis, elevated transaminases, and cholangitis. For drugs with enterohepatic circulation, excretory abnormalities may overlap with enhanced reabsorption, making it difficult to rapidly reduce exposure through simple dose reduction. Chronic toxicity often has an insidious onset and delayed manifestation. Without prospective evaluation of excretory function and steady-state concentrations, exposure issues may only become apparent after years of treatment.

4 Clinical Medication Optimization Strategies Based on Pharmacokinetic Characteristics

The optimization of drug administration based on pharmacokinetic characteristics fundamentally involves shifting from a "fixed-dose mindset" to an "exposure-targeted approach." At the dose design level: (1) Leveraging early pharmacokinetic/pharmacodynamic models and population pharmacokinetic analyses to quantify the contributions of absorption, distribution, metabolism, and excretion to exposure, and setting target concentration ranges and dosing intervals by combining exposure-therapeutic and exposure-toxicity curves; (2) During administration, incorporating key covariates such as body weight, age, organ function, and concomitant medications into dose estimation to align the initial dose with individual pharmacokinetic profiles, while predefining laboratory monitoring protocols at critical time points to promptly identify trends of excessive or insufficient exposure; (3) For drugs with narrow therapeutic windows or significant exposure variability, implementing therapeutic drug monitoring (TDM) by integrating concentration measurements with model predictions to achieve bidirectional "concentration-dose" calibration, gradually converging toward individualized maintenance regimens, thereby ensuring therapeutic efficacy while controlling long-term toxicity risks.

5 Conclusion

The pharmacokinetic characteristics of drugs establish a continuous logical chain linking dosage, exposure, and clinical outcomes: the rate and extent of absorption shape the onset of action and the starting point of exposure, the distribution pattern determines targeting and the burden on non-target organs, while the metabolic and excretory processes collectively control the duration of therapeutic efficacy and the potential for toxic accumulation. Systematic analysis centered on this chain enables a quantitative re-evaluation of the intrinsic relationships between suboptimal efficacy, acute adverse reactions, and chronic toxicity. Future advancements in integrating and visualizing pharmacokinetic information during drug development, population modeling, and clinical decision support, combined with the continuous accumulation of therapeutic drug monitoring and real-world data, hold promise for constructing more flexible and actionable personalized dosing systems. This will facilitate a more robust balance between "precision and efficacy" and "long-term safety" in drug therapy.

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