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ADME PROCESSES: FUNDAMENTAL PRINCIPLES OF DRUG ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

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Annotation: The ADME (Absorption, Distribution, Metabolism, Excretion) processes are fundamental pharmacokinetic mechanisms determining the fate of drugs in the human body. These processes influence drug bioavailability, therapeutic efficacy, toxicity, and interindividual variability in drug response. This article reviews the main principles governing each ADME phase, including physicochemical drug properties, transport mechanisms, plasma protein binding, metabolic pathways mediated by cytochrome P450 enzymes, and renal and hepatic elimination. Clinical implications, such as drug interactions, altered pharmacokinetics in special populations, and strategies for optimizing therapy, are discussed. Understanding ADME processes is essential for rational drug design, personalized therapy, and effective pharmacological management.

Keywords: ADME, pharmacokinetics, absorption, distribution, metabolism, excretion, bioavailability, cytochrome P450, renal clearance, drug interactions.

Pharmacokinetics describes how the body affects a drug through absorption, distribution, metabolism, and excretion—collectively termed ADME. These processes determine plasma and tissue drug concentrations over time and ultimately influence therapeutic and toxic effects. Comprehensive knowledge of ADME principles allows clinicians and pharmacologists to predict drug behavior, adjust dosages, avoid adverse effects, and minimize interactions. Each ADME phase is governed by a combination of physicochemical properties, enzymatic activity, transporter function, and patient-specific factors such as age, genetics, and organ function.

Drug absorption refers to the passage of a drug from the site of administration into systemic circulation. The efficiency of absorption is influenced by solubility, ionization (pKa), formulation, gastrointestinal pH, presence of food, and transit time. Transport mechanisms include passive diffusion, facilitated diffusion, active transport, and endocytosis. Bioavailability, defined as the fraction of administered drug reaching systemic circulation, varies by route; intravenous administration achieves 100%, whereas oral drugs often undergo first-pass metabolism in the liver, reducing systemic exposure. Clinical examples include reduced absorption of weakly basic drugs due to proton pump inhibitors and chelation of tetracyclines with divalent cations.

Distribution refers to the reversible transfer of drugs between systemic circulation and tissues. Plasma protein binding to albumin, α1-acid glycoprotein, and lipoproteins affects free drug

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concentrations and therapeutic activity. The volume of distribution (Vd) reflects the theoretical space into which a drug distributes and is critical for calculating loading doses. Tissue permeability depends on lipophilicity, molecular size, and the presence of barriers such as the blood–brain barrier. Active transporters, including P-glycoprotein, modulate tissue distribution, while pathological states like inflammation or hypoalbuminemia can alter drug distribution.

Drug metabolism transforms lipophilic compounds into more hydrophilic metabolites for excretion. Phase I reactions involve oxidation, reduction, or hydrolysis, mainly mediated by cytochrome P450 enzymes such as CYP3A4, CYP2D6, and CYP2C9. Phase II reactions conjugate drugs with glucuronic acid, sulfate, or glutathione, enhancing solubility. Metabolism can activate prodrugs, inactivate active drugs, or produce toxic metabolites. Factors affecting metabolism include genetic polymorphisms, enzyme induction or inhibition, age, liver disease, and co-administered drugs. Altered metabolism can result in therapeutic failure or toxicity, highlighting the importance of pharmacogenetics and monitoring.

Excretion removes drugs and metabolites from the body, primarily via renal and hepatic routes. Renal excretion involves glomerular filtration, active tubular secretion, and passive reabsorption; urine pH affects ionized drugs' elimination. Biliary excretion allows drugs and metabolites to be secreted into bile, sometimes undergoing enterohepatic recycling, which prolongs half-life. Other routes include pulmonary excretion of volatile drugs and minor routes via sweat, saliva, and breast milk. Impaired renal or hepatic function necessitates dosage adjustments to avoid accumulation and toxicity.

ADME processes have critical implications for therapeutic outcomes. Drug interactions occur when one drug affects the absorption, metabolism, distribution, or excretion of another. Special populations such as neonates, the elderly, and patients with organ dysfunction exhibit altered pharmacokinetics. Therapeutic drug monitoring is crucial for drugs with narrow therapeutic windows. Understanding physicochemical properties, transporter interactions, and metabolic pathways enables formulation strategies such as modified-release preparations or targeted delivery systems to optimize therapy.

ADME processes determine the pharmacokinetic and pharmacodynamic profiles of drugs. Comprehensive understanding allows clinicians to optimize dosing, minimize adverse effects, and anticipate drug interactions. Advances in pharmacogenomics and drug delivery continue to refine our understanding of absorption, distribution, metabolism, and excretion, supporting more effective and personalized pharmacotherapy. Knowledge of these processes is essential for safe and rational drug use, ensuring maximum therapeutic benefit while reducing risks.

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