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PHARMACOKINETIC DRUG–DRUG INTERACTIONS: PHYSIOLOGICAL CHANGES ARISING FROM CONCURRENT ADMINISTRATION OF MULTIPLE MEDICATIONS

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Annotation: This article explores the mechanisms and clinical implications of pharmacokinetic drug–drug interactions that occur when multiple medications are administered simultaneously. Such interactions influence absorption, distribution, metabolism, and excretion, resulting in altered plasma concentrations, therapeutic effects, or toxicity. The analysis discusses the molecular and physiological determinants of drug interactions, including transporter proteins, metabolic enzyme systems, protein-binding dynamics, and renal clearance mechanisms. Special attention is given to cytochrome P450 isoenzymes, P-glycoprotein modulation, and genetic variability affecting drug disposition. The article also examines high-risk clinical scenarios, factors predisposing patients to interactions, and strategies for prevention and monitoring. Overall, this work clarifies the essential principles of pharmacokinetic interactions and highlights their significance in optimizing safe and effective pharmacotherapy.

Keywords: pharmacokinetics, drug–drug interactions, CYP450 enzymes, absorption, metabolism, excretion, P-glycoprotein, plasma concentration, renal clearance, therapeutic safety

Modern medical practice increasingly involves complex therapeutic regimens in which patients receive multiple medications. While polypharmacy may be necessary for managing chronic or comorbid conditions, it also increases the risk of drug–drug interactions capable of altering pharmacokinetics and, consequently, clinical outcomes. Pharmacokinetic interactions modify how the body handles a drug rather than how the drug affects the body, influencing each of the four key phases—absorption, distribution, metabolism, and excretion.Understanding these processes is essential for preventing adverse reactions, optimizing dosing, and ensuring therapeutic efficacy. This article provides a comprehensive overview of the mechanisms behind pharmacokinetic interactions, their clinical relevance, and their implications in different patient populations.

Drug absorption may be significantly affected by changes in gastric pH or intestinal motility. Antacids, proton-pump inhibitors, and H2-blockers can alter the solubility of weakly basic or acidic drugs, reducing or increasing their bioavailability. Similarly, drugs that affect gastrointestinal motility—such as metoclopramide or opioids—can accelerate or delay absorption.Some medications form insoluble complexes when combined. For instance, tetracyclines and fluoroquinolones bind with calcium or magnesium supplements, reducing their absorption. This mechanism is common with multivalent ions found in antacids, supplements, and certain foods.

Membrane transporters such as P-glycoprotein (P-gp) regulate drug efflux in the gut. Inhibitors of P-gp (e.g., clarithromycin, verapamil) increase absorption of P-gp substrates, while inducers decrease systemic exposure. This interaction is particularly relevant in drugs with narrow therapeutic indices.

Drugs that bind to plasma proteins such as albumin can compete for binding sites. Highly protein-bound medications (warfarin, valproic acid, NSAIDs) may be displaced by other agents, leading to increased free drug concentration and enhanced pharmacologic effect. Although displacement alone rarely causes severe toxicity, it may contribute significantly when combined with metabolic inhibition.

Interactions affecting blood flow or vascular resistance may alter drug distribution. For example, vasodilators or cardiac medications may enhance perfusion in certain organs, influencing the delivery and distribution of co-administered drugs.Transport proteins in the blood–brain barrier, liver, and kidneys also influence distribution. Inhibition or induction of transporters such as OATP, BCRP, or MRP can modify tissue uptake and systemic exposure.

Metabolism is the most clinically significant pathway for pharmacokinetic interactions. The CYP450 enzyme family—particularly CYP3A4, CYP2D6, CYP2C9, and CYP1A2—plays a central role in drug biotransformation.Enzyme inhibition reduces metabolic clearance, increasing plasma concentration and prolonging drug action. Potent CYP inhibitors include:

ketoconazole, itraconazole

ritonavir and other protease inhibitors

macrolide antibiotics

fluoxetine, paroxetine

amiodarone, verapamil

Inhibition may result in dangerous toxicity, especially for drugs metabolized through a single dominant pathway.

Inducers accelerate metabolism, lowering drug concentrations and reducing therapeutic effect. Major inducers include:

rifampicin

carbamazepin

phenytoin

St. John’s wort

Induction often requires several days to develop, and its effects may persist after discontinuation.

Interactions involving glucuronidation or acetylation can alter clearance of medications such as lamotrigine, morphine, and isoniazid. Although less common than CYP interactions, these effects remain clinically important.

Genetic polymorphisms in metabolic enzymes significantly influence susceptibility to interactions. Poor metabolizers may experience toxicity, while ultra-rapid metabolizers may fail to achieve therapeutic levels.Many medications depend on renal excretion. Interactions can occur at various steps:

glomerular filtration

active tubular secretion

tubular reabsorption

Competition for renal transporters (e.g., between NSAIDs and methotrexate) may lead to increased toxicity.Drugs that alkalinize or acidify urine can modify excretion of weak acids or bases. For example, urinary alkalinization enhances elimination of phenobarbital or salicylates.ACE inhibitors, diuretics, and NSAIDs can alter renal blood flow and impact clearance of other medications. This is particularly relevant in elderly patients or those with chronic kidney disease.

Age-related physiological changes and multiple comorbidities increase vulnerability to interactions. Reduced hepatic function, diminished renal clearance, and altered protein binding are key contributing factors.Patients with liver or kidney disease, cardiovascular disorders, diabetes, or psychiatric conditions frequently require complex medication regimens, raising interaction risks.Pregnant women, children, and genetically distinct populations may metabolize drugs differently, necessitating increased monitoring.

Clinicians should consider pharmacokinetic profiles before combining medications, especially those with narrow therapeutic windows such as warfarin, digoxin, lithium, or immunosuppressants.

Measurement of plasma concentrations is essential for managing interactions involving anticonvulsants, antibiotics, and certain psychotropic medications.

Patients should understand the importance of adhering to prescribed regimens, avoiding unsupervised supplements, and reporting new medications.

Pharmacokinetic drug–drug interactions represent a critical consideration in modern pharmacotherapy. As therapeutic regimens grow more complex, understanding the mechanisms by which drugs affect each other's absorption, distribution, metabolism, and excretion becomes increasingly important. These interactions can profoundly alter drug exposure, efficacy, and safety. Early recognition, informed prescribing, and close monitoring help clinicians minimize risks and ensure optimal outcomes. Ultimately, mastery of pharmacokinetic interaction principles is essential for safe and effective patient care in all medical specialties.

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