

Drug Interactions and Their Mechanisms: A Comprehensive Review

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ABSTRACT:

This comprehensive article explores the complex landscape of drug interactions, encompassing various aspects such as pharmacokinetic and pharmacodynamic mechanisms, drug absorption, distribution, metabolism, and excretion interactions. The discussion extends to interactions with food, alcohol, herbs, smoking, and their implications in different disease conditions. The article emphasizes the importance of understanding these interactions to navigate potential risks and optimize therapeutic outcomes. It concludes by highlighting the significance of considering drug interactions in both diagnosis and prescription changes, with an emphasis on personalized formularies and clinical pharmacology principles.

KEY WORDS: Interactions, Pharmacokinetic, Pharmacodynamic..

I. INTRODUCTION:

An interaction occurs when the effect of one drug is changed by the presence of another drug, food, herbal medicine or by some environmental chemical agent. The common causes of drug interaction include multiple drug therapy, multiple disease, wrong choice of drug, failing to take account of renal function, wrong dosage and route of administration, errors in taking the drug and poor patient compliance. The drug whose activity is affected by an interaction is called as 'object drug'. The agent which precipitates such an interaction is called as 'precipitant'. Understanding the potential reactions of drug interaction and their mechanism helps us to navigate the serious effects of combining drugs with other mechanism, food, herbs and vitamins with confidence.^[1]

II. DRUG-DRUG INTERACTIONS: PHARMACOKINETIC MECHANISM OF DRUG-DRUG INTERACTIONS:

Pharmacokinetic interactions occur when one drug changes the systemic concentration of other. This type of interactions is those in which

ADME properties of object drug is altered by the precipitant.

DRUG ABSORPTION INTERACTION: Several factors may influence the drug interaction. The first factor is changes in gastrointestinal pH. Most of the drugs orally administered needs to be absorbed and dissolved in the gastric pH between 2.5 and 3. Therefore drugs able to increase gastric pH can change the absorption of drugs that are absorbed in an acidic environment. For example: Absorption of antifungal drug itraconazole is decreased when taken with an antacid which increases the pH of the stomach. In contrast giving in enteric Aspirin with a drug that increases the pH such as ranitidine can cause the enteric coating to dissolve in the stomach instead of intestine.^{[2][3]}

Another mechanism involves changes induced by its chelation and adsorption. For example, combination of antibiotics such as ciprofloxacin, tetracycline with iron or calcium supplement results in lower drug absorption. Cholestyramine and colestipol bind bile acids and prevent their absorption in digestive tract but they can also bind other drugs mainly acidic drugs. (Example: warfarin, sulfonamides, furosenamide). Therefore the interval between the administration of bile acid sequestrants and other drugs may be as long as possible (preferably 4h).^{[2][3]}

The third factor is changes in GI motility. Since most of the drugs absorbed in the upper part of the small intestine, drugs that alter the movement of GI tract may affect the rate of absorption. For eg: metoclopramide may increase the gastric emptying time hence decreasing the absorption of digoxin and theophylline, whereas it can increase the absorption of alcohol, acetylsalicylic acid, tetracycline, acetaminophen and levodopa.^{[2][3]} Cell transporter such as p-glycoprotein may also contribute to absorption DDI. p-glycoprotein regulates the intestinal absorption of drugs and promote their excretion. Therefore administration of drugs that are able to



stimulate or inhibit the activity of p-glycoprotein can cause DDI. For example: when cyclosporine is given along with sirolimus p-gp activity is reduced. Hence less drug pumped back into intestine, more cyclosporine remains in the body which leads to possible kidney damage.^{[2][3]}

DRUG DISTRIBUTION INTERACTION: One factor that affects drug distribution is extent of binding with plasma and tissue proteins. Of the many plasma proteins the most important are albumin, α -1-acid glycoprotein and lipoproteins. Protein bound drugs are not available to exert pharmacological effects, only the portion of drug that is not protein bound is available for diffusion to the tissue site and pharmacological effects. For example: warfarin and diclofenac have same affinity for albumin. Therefore, coadministration of these drugs results in displacement of warfarin from its binding site. The increase in plasma concentration of free warfarin causes the development of serious hemorrhagic reactions.^{[2][3]}

DRUG METABOLISM INTERACTIONS: The major drug metabolizing enzymes are cytochrome p-450 enzymes. More than 50 cytochrome p450 enzymes have been identified but only 6 are involved in DDI (CYP2C9, CYP2C19, CYP1A2, CYP2E1, CYP3A4, CYP2D6). Metabolism DDIs can occur when a drug that affect activity or production of CYP enzymes is given with a drug that are metabolized by CYP enzyme.^[3] The drug metabolized by CYP enzyme is called as 'substrate'. Drugs that inhibit the activity of CYP enzymes are called as 'inhibitors' which increase the effect of substrate drug. e.g.: when theophylline which is a substrate of CYP1A2 is given with cimetidine, theophylline levels may increase to toxic concentration because cimetidine inhibits the effects of CYP1A2 and leads to slower metabolism of theophylline.^[3]

Drugs that cause the production of larger amount of enzymes are called as 'inducers' which decrease the effect of substrate. Eg: if a patient begins smoking while taking theophylline, theophylline levels decreases to sub-therapeutic level because tobacco produce more CYP1A2 and leads to Quicker metabolism of theophylline.^[3]

DRUG EXCRETION INTERACTIONS: Drugs that are excreted by the kidney can get involved in drug interactions by different mechanism such as competition at active transport sites or alterations in glomerular filtration, tubular secretion, tubular

reabsorption and urinary PH.^[3] Glomerular filtration is affected by many factors. Drugs such as NSAIDS (e.g. ibuprofen) can reduce the GFR resulting in slowed excretion of drugs that are eliminated by the kidneys. Aminoglycoside antibiotics (e.g. gentamicin) are eliminated almost entirely by kidney. The blood levels of aminoglycoside must be carefully monitored in patients with reduced GFR to reduce toxicity.^[3]

Drugs can compete with each other for secretion. e.g. probenecid is sometimes given with oral penicillin to increase penicillin drug levels because both the drug compete for the same cellular transporters in the tubule. Erythromycin inhibit p-gp which leads to increase in p-gp substrates such as digoxin by preventing the secretion of the digoxin into the tubule.^[3] Excretion of drugs can also be affected by changing the pH of the urine. Weakly acidic drugs become more ionized in alkaline urine (high pH). Ionized drugs are not reabsorbed into the blood and are excreted in the urine .eg: Changes in excretion of Aspirin due to alterations in urinary pH caused by antacids.^[3]

PHARMACODYNAMIC MECHANISM FOR DRUG-DRUG INTERACTIONS:

Pharmacodynamics DDIs occur when the effect of one drug is altered by the other drug when drugs or given in a combination regimen. The combined effects of drug results in additive, antagonistic or synergistic effect.^{[3][4]} Additive interactions occur when the effect of combining drug is greater than the effect of each drugs given alone .example: when alcohol is taken along with sleep medicines, it cause increased drowsiness, greater than the drowsiness that is caused either by alcohol or sleep medicine.^{[3][4]} Antagonistic interaction occur when one drug reduces the effect of other. Example: acetylcysteine is used to treat acetaminophen overdose which eliminates the toxic metabolites of acetaminophen and prevents the toxic effect on the liver.^{[3][4]} Synergistic interaction occur when the combined effect of two drug exceeds the sum of the effects of each step given alone. Example :Aminoglycosides such as gentamicin and penicillin's such as ampicillin are often given for serious infections in hospitalized patients.^{[3][4]}

III DRUG-FOOD INTERACTIONS :

Drug food interactions occur when the drug reacts with food or beverages. The mechanism of food induced interactions are same as that of

drug interactions, however these occurs mainly due to alterations in absorption that may impair that nutritional benefit and some may be due to altered metabolism.^{[8][13]}

PHARMACOKINETIC MECHANISM FOR DRUG-FOOD INTERACTION:

DRUG ABSORPTION INTERACTION: Food may alter the drug absorption by altering GI pH, gastrointestinal motility and transit time. Eg: Absorption of Azithromycin is decreased when it is taken with food which leads to reduction in bioavailability. Components of food such as calcium or iron forms complexes with drugs which affect drug absorption. Eg: Tetracycline, sodium fluoride and ciprofloxacin.^[5]

DRUG METABOLISM INTERACTION: Food alters the metabolism of some drugs. Eg: grapefruit juice blocks cytochrome P450 and 1A2 enzymes. Hence it should not be taken with antihypertensive drugs, cyclosporin, antimalarial drugs, anti-anxiety drugs which are mainly metabolized by these enzymes. The reason is that the grapefruit juice can cause higher levels of these medicines in the body which leads to side effects or toxicity.^[6]

DRUG EXCRETION INTERACTION: The half-life of certain drugs is altered by change in urinary pH due to food. The half-life of acidic drugs is extended in acidic urine and the half-life of acidic drug is reduced in alkaline urine. Foods such as milk, citrus fruit can alkalize the urine. Meats, fish, eggs can acidify the urine.^[5]

PHARMACODYNAMIC MECHANISM FOR DRUG-FOOD INTERACTION:

Food may interact with medications by altering their pharmacologic actions. Eg: anti-coagulant warfarin antagonizes vitamin k which leads to depletion of active vitamin k. When green leafy vegetables or 'greens' are taken with warfarin which is having large amount of vitamin k causes reversal of its depletion.^{[7][14]}

IV. TAKING DRUGS WITH ALCOHOL:

Alcohol and drugs can affect each other ADME. Alcohol can increase drug absorption by enhancing gastric solubility of drugs and by increasing GI blood flow. Acute intake of alcohol inhibits the metabolism of many drugs and can induce liver enzymes to metabolise drugs more efficiently. Eg: taking alcohol with Metronidazole

can cause flushing, headache, palpitations, nausea and vomiting.^[6]

V. HERB-DRUG INTERACTIONS:

Herb-drug interactions can occur through the synergistic or additive actions of herbal products with medications. The most well-known example is the interaction of St John's wort(hypericum perforatum).with variety of drugs. St John's wort can induce the cytochrome p450 isoenzyme CYP3A4 and also induce p-glycoprotein. Many herbs such as echinacea, kava, garlic and natural compounds isolated from herbs like flavonoids, caffeine, coumarin are substrate inhibitors or inducers of various CYP enzymes.^[9] A few pharmacodynamic interactions are also identified. Pharmacodynamic interactions may be synergistic like interactions between anticoagulant warfarin with anti-platelet herbs or antagonistic like Kava reduces the pharmacological activity of anti-Parkinson drug levodopa.^{[9][10]}

VI DRUG INTERACTIONS WITH SMOKING:

Cigarette smoking remains highly prevalent in many countries. It can affect drugs by both pharmacokinetic and pharmacodynamic mechanism. The mechanism involved in most interactions between smoking and drugs involves induction of metabolism. Nicotine induces the activity of several enzymes including CYP 2E1/2A2 and CYP 2B1/2B2 and high inducibility is more common in patients with lung cancer. Drugs which get induced by smoking includes theophylline, caffeine, imipramine, haloperidol, propranolol, flecainide and estradiol. Pharmacodynamic interactions have also been described. Eg: Smoking causes decrease in blood pressure and heart rate during treatment with beta blockers, less sedation from benzodiazepines and less analgesia from opioids reflecting the effects of stimulant actions of nicotine.^{[11][15]}

VII DRUG DISEASE INTERACTIONS:

Drug disease condition interaction may occur when an existing medical condition makes certain drugs potentially harmful. Some of the drug disease interactions includes when thiazides is given in patients with gout, it may cause worsening of gout, when NSAIDs is given for patients who have decreased renal function it may lead to renal failure, when antipsychotics other than quetiapine or clozapine is given in Parkinson disease patients it may lead to worsening of Parkinson disease symptoms.^{[12][16]}

II. CONCLUSION:

DDIs represent a common clinical problem during the management of patients treated with several drugs. Drug interaction should be considered both in diagnosis of symptoms and when prescription changes are made. Software checker for DI are widely available. Patient harm from drug interaction can be reduced by using a personal formulary, recognizing drugs that are majorly involved in interactions, recognizing narrow therapeutic index drugs that are vulnerable to interactions and applying clinical pharmacology principles.

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