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(REVIEW ARTICLE)

A review on drug interaction

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Abstract

Drug interaction occur when the response of one drug is altered by the simultaneous or closely time administration of another drug. Polypharmacy involving the simultaneous use of multiple drugs, raise concern due to unpredictable and potential severe internation. While some drug interactions are intentionally utilized in therapeutics strategies, their severity can vary making prediction challenging. Prescribing multiple medications increases the risk of drug interactions, which can occur with other drugs, foods, beverages, and herbs, both inside and outside the body. Understanding in vitro interactions is crucial to prevent drug activity loss before administration. While not all theoretical drug interactions may occur in practice, they remain a significant cause of adverse events associated with drug administration. Drug-drug interactions (DDIs) represent a significant source of medication errors in developed nations, especially among the elderly who often take multiple medications simultaneously, leading to a prevalence of 20-40%. The complexity of managing therapy increases with poly-therapy, elevating the risk of clinically significant DDIs that can either trigger adverse drug reactions or diminish clinical efficacy. DDIs are typically categorized into two groups: pharmacokinetic and pharmacodynamic. In vivo interactions at pharmacokinetic level affect absorption, distribution, biotransformation or excretion of drugs. Induction or inhibition of cytochrome P450 (CYP450) enzymes forms a major basis of drug interactions. Induction of metabolism of a substrate drug leads to treatment failure.

Keywords: Adverse Drug Reaction; Absorption; Distribution; Metabolism; Drug-Drug Interactions; Excretion; Biotransformation; Poly-Therapy

1. Introduction

Drug interactions, particularly drug-drug interactions, happen when one medication influences the response to another when they are used together or in proximity. This impact can primarily be quantitative, changing the strength of the response, but occasionally it can be qualitative, leading to unusual or different reactions. When a patient is on multiple medications, the potential for drug interaction exists, and this risk grows with the number of medications used. Numerous medical conditions necessitate treatment with a combination of drugs. These combinations are selected carefully to enhance each other's effects. For instance, antibiotics might be combined with pain relievers to treat an infectious ailment, or adrenaline could be paired with lidocaine for local anesthesia. Similarly, a mixture of antimicrobials might be prescribed for mixed bacterial infections. Patients with multiple conditions, like hypertension and diabetes, often receive multiple medications, which can increase the risk of unintended or adverse drug interactions due to the variety of drugs used for their specific conditions. Certain drug interactions are deliberately employed in treatment, such as the synergistic effect of combining ACE inhibitors and diuretics for hypertension, sulfamethoxazole with trimethoprim for bacterial infections, or furosemide with amiloride to prevent hypokalemia. The intentional interactions are carefully designed and deemed safe. However, the primary concern lies with drug interactions that can disrupt treatment outcomes, lead to adverse effects, or potentially result in fatalities (such as excessive bleeding from anticoagulants). The severity of these interactions can often be unpredictable. Hence, it's vital for doctors to be aware

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of which drugs should not be prescribed together to minimize these risks. While there are numerous instances where drug interactions are beneficial and effectively used to enhance the effectiveness of drugs in treating infections, managing pain, and addressing cardiovascular issues, there are also hundreds of drug interactions considered unfavorable "(1)".

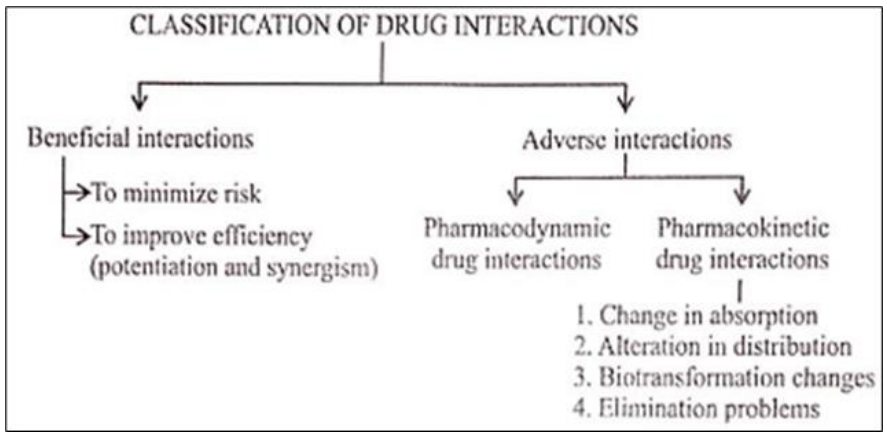

Figure 1 Classification of drug interaction

Drug interaction is

- Mostly undesirable (harmful) eg- Iron salt and tetracycline
- Rarely desirable (beneficial) eg- Enhancement of activity of penicillin when administered with probenecid

1.1. Drug interaction broadly classified into two types

1.1.1. Pharmacokinetics internation

Absorption internation, Distribution interaction, Metabolism interaction, Excretion interaction

1.1.2. Pharmacodynamic internation

- Direct pharmacodynamic interaction
- Indirect pharmacodynamic interaction

1.2. Pharmacokinetics interaction: -Pharmacokinetics is 'what the body does to the drug' "(2)".These interactions occur when one drug alters the concentration of another drug

A pharmacokinetic drug interaction occurs when one drug affects how another drug absorbed, distributed, metabolized, or excreted (ADME). (Fig .2) This interaction is assessed by changes in various kinetic parameters, such as maximum serum concentration, half-life, amount excreted in urine, and area under the concentration-time curve.

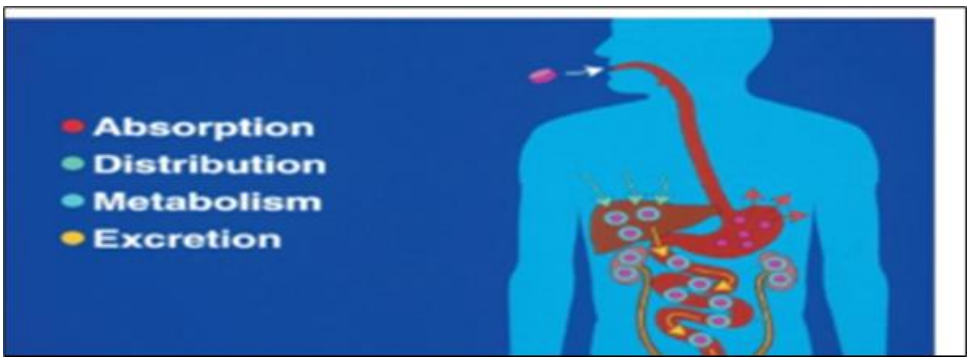

Figure 2 ADME process

2. Absorption

Drug absorption can be influenced by various factors, including

- Gut motility, Gut pH, Drug solubility, Gut metabolism, Gut flora, Activity of protein carriers."(3)".

Drug absorption can be affected by changes in gastrointestinal motility caused by drugs. The small intestine is where most drugs are primarily absorbed. Altering the rate at which a drug reaches this part of the gastrointestinal tract can impact its absorption rate. Drugs that inhibit peristalsis (like narcotics such as morphine and anticholinergic agents like atropine) can prolong the transit time of the drug in the intestine, thereby increasing the absorption time. One key factor is the alteration in gastric ph. Most orally administered drugs need a gastric pH between 2.5 and 3 for dissolution and absorption. Thus, drugs that raise gastric pH (like antacids, anticholinergics, proton pump inhibitors [PPIs], or H2-antagonists) may reduce the absorption of drugs such as ketoconazole and itraconazole, which are absorbed best in an acidic environment "(4)".Indeed, H2 antagonists (like ranitidine), antacids (such as aluminum hydroxide and sodium bicarbonate), and PPIs (like omeprazole, esomeprazole, and pantoprazole) that elevate gastric pH can reduce the bioavailability of cefpodoxime. However, they can also aid in the absorption of beta-blockers and tolbutamide. "(5)".Interactions between food and drugs can impact the bioavailability of a drug. The bioavailability of a drug, which is linked to its effectiveness, can be altered by food-drug interactions through chemical reactions like chelation or physiological responses to food intake. These interactions may involve changes in gastric acidity, bile secretion, and gastrointestinal motility. "(6)".

P glycoprotein: An additional method of changing drug absorption is through the activity of a membrane-bound carrier protein found in many tissues, particularly in organs responsible for drug absorption and elimination. P-glycoprotein (P-gp) is a well-known adenosine triphosphate (ATP)-dependent carrier glycoprotein located in the plasma membrane. It plays a role in actively transporting a broad range of endogenous and exogenous substances across various membranes in the intestines, proximal tubules of the kidneys, brain, and testes."(7,8)". Among the interactions investigated during the time of this review, notable mentions include the impact of terfenadine on the transport of doxorubicin, as well as the effects of chlorpromazine and progesterone on the transport of cyclosporine. "(9)".The interactions involving P-gp inhibitors could potentially lead to a clinical impact when these inhibitors are combined with medications with a narrow therapeutic index (such as digoxin, theophylline, and anticancer drugs). Examples of these P-gp inhibitors include macrolides (like erythromycin, roxithromycin, and clarithromycin), PPIs (such as omeprazole or esomeprazole), and anti-arrhythmic drugs (like dronedarone, amiodarone, verapamil, or diltiazem) "(10)".

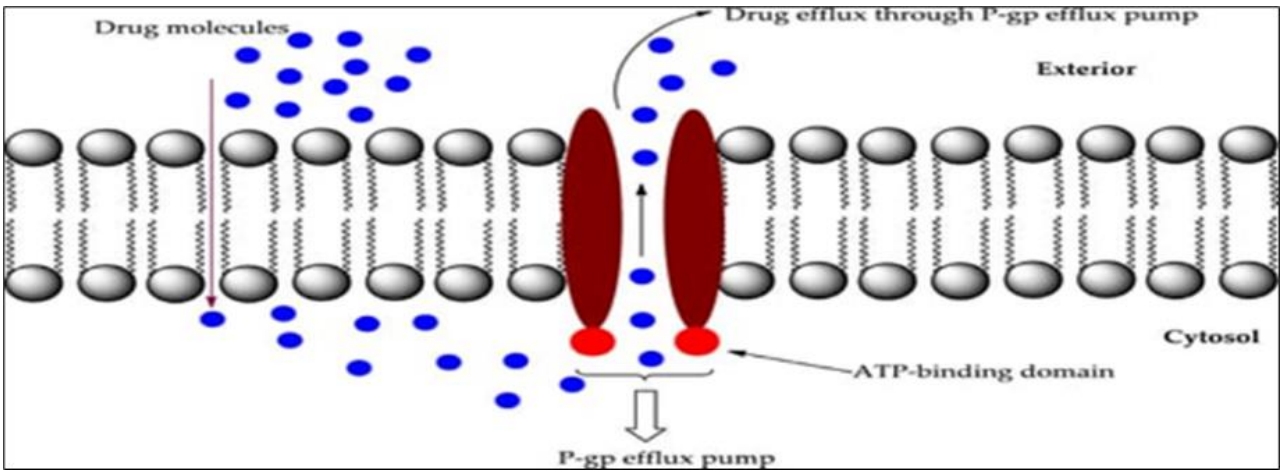

Figure 3 P glycoprotein

3. Distribution

Typically, drugs are transported by binding to plasma and tissue proteins. Among the various plasma proteins that interact with drugs, the most crucial ones include albumin, α1-acid glycoprotein, and lipoproteins. Acidic drugs tend to bind more extensively to albumin, On the other hand, basic drugs tend to bind more extensively to α1-acid glycoprotein, lipoproteins, or both. It's important to note that only the unbound (free) drug is available for passive diffusion to extravascular or tissue sites. This unbound drug typically determines the drug concentration at the active site, influencing its efficacy. Albumin is the predominant protein in plasma, synthesized in the liver, and distributed in both plasma and extracellular fluids of skin, muscles, and various tissues. The concentration of albumin in intestinal fluid is approximately 60% of that in the plasma. Albumin has five binding sites, including those for warfarin, benzodiazepines, digoxin, bilirubin, and tamoxifen, with the main ones characterized as site I and II. "(11)". As molecules interact with their molecular targets and undergo metabolism, additional molecules enter the solution to reach the site of action. The extent of plasma protein binding, indicated by the ratio of bound drug concentration to free drug concentration, varies significantly among drugs. This ratio can reach high values, especially when it exceeds 0.9, while ratios below 0.2 are considered low. Drugs with a strong binding to plasma proteins are at a higher risk of being displaced by other drugs that have a stronger affinity for the same binding site. When warfarin and diclofenac are given together, a common pharmacological effect occurs. Since both drugs have a similar affinity for albumin, when diclofenac is given to a patient already taking warfarin, it displaces the warfarin from its binding site. This displacement leads to an increase in the concentration of free warfarin in the blood, which can result in serious bleeding reactions. "(5)".

4. Metabolism

The area of biotransformation, also known as metabolism, is exploding with new information. Recent studies indicate that the most clinically significant drug interactions typically involve metabolic pathways. Many drugs are removed from the body by being chemically transformed into less lipid-soluble forms, which prevents their reabsorption across lipid membranes. These transformed products are then excreted by the kidneys or in the bile. While drug metabolism can occur in various locations such as the plasma, intestines, lungs, and skin, the primary site is the smooth endoplasmic reticulum of the hepatocyte. It seems like you're referring to the two phases of drug metabolism. (fig .4) Here's a breakdown:

- **Phase I Metabolism:** Involves oxidation, hydrolysis, or reduction of a drug. These reactions increase the water solubility of the drug, making it easier for the body to eliminate. Phase I reactions include processes like oxidation, reduction, and hydrolysis.
- **Phase II Metabolism:** Involves the attachment of an additional molecule to the drug, creating an inactive compound and a more water-soluble drug. Phase II processes include:
  - Glutathione Conjugation: Attachment of glutathione to the drug.
  - Glucuronidation: Attachment of glucuronic acid.
  - Sulfation: Attachment of a sulfate group.
  - Acetylation: Attachment of an acetyl group.
  - Methylation: Attachment of a methyl group.

These Phase II processes further increase the water solubility of the drug, aiding in its elimination from the body.

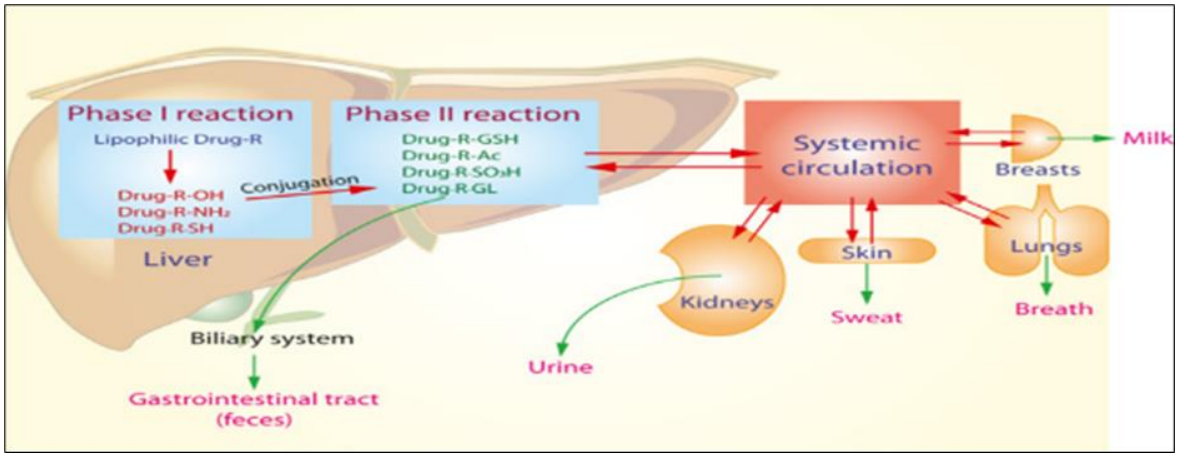

Figure 4 Phase I & phase II metabolism

The enzyme referred to as hepatic CYP is a cytochrome P450 enzyme, which is a complex of protein, heme, and iron. This enzyme system uses molecular oxygen and NADPH as a source of electrons to catalyze oxidation-reduction reactions, resulting in the oxidized drug product "(13)".There are over 50 different families of cytochrome P450 enzymes identified, with CYP1, CYP2, and CYP3 being the major families responsible for metabolizing a wide range of compounds including steroids, prostaglandins, vitamins, and drugs. These families have various subfamilies, such as CYP1A, CYP2D, and so on, each with specific functions in drug metabolism. Enzymes within a family are identified by a capital letter, and individual enzymes have a final Arabic number, such as CYP2C9 and CYP2C19, which belong to the CYP2 family and the CYP2C subfamily. If two drugs are metabolized by the same enzyme, they could potentially interact, competing for the enzyme. This competition could result in one drug being metabolized while the other's metabolism is reduced, leading to higher levels of the non-metabolized drug in the blood. To predict a clinically significant drug interaction involving the CYP system, it's important to know the substrates (compounds metabolized by the enzyme), inhibitors (drugs that interfere with the enzyme), and inducers (agents that speed up the metabolism of a substrate). "(3)".

The rate of drug metabolism may be increased or decreased based on enzyme induction or enzyme inhibition. Induction of drug metabolism usually occurs by enhanced gene transcription following prolonged exposure to an inducing agent (Fig. 5)

4.1. Metabolic induction

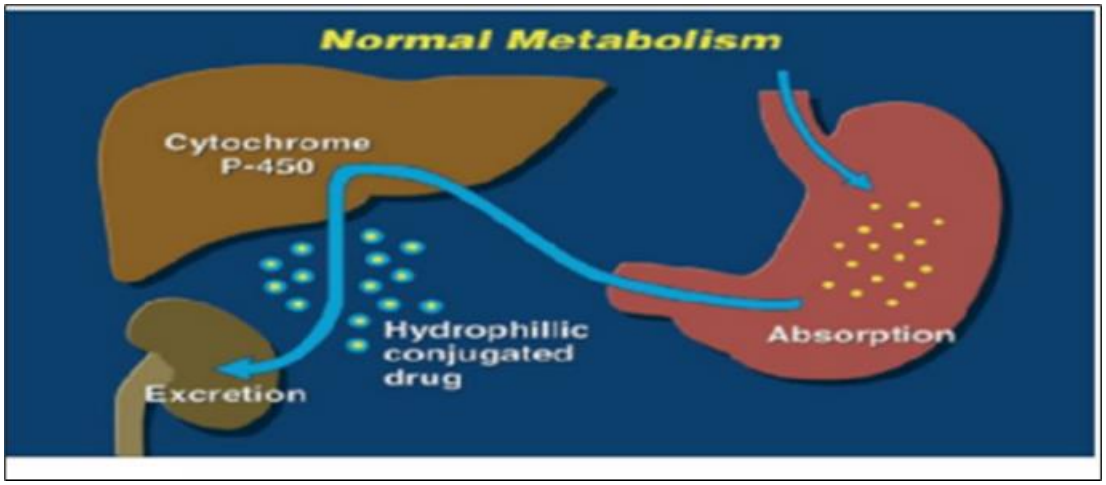

Figure 5 Normal metabolism

Drug interactions involving enzyme induction are not as common as inhibition-based drug interactions but equally profound and clinically important. Exposure to environmental pollutants as well as the large number of lipophilic drugs can result in induction of CYP enzymes. he most common mechanism is transcriptional activation leading to increased synthesis of more CYP enzyme proteins. "(16)".The effect of induction is simply to increase the amount of P450 present and speed up the oxidation and clearance of a drug. "(17)".The most commons enzyme inducers are rifampicin "(18,19,20)".phenobarbital "(21,22)".phenytoin "(22,23)".carbamazepine "(23, 24,25)".and anti-tubercular "(24)". drugs. Recently, we documented in a patient with epilepsy a DDI between phenobarbital and lamotrigine that induced the development of leukopenia and thrombocytopenia. We postulated that CYP enzyme induction by phenobarbital could be responsible for the production of reactive metabolites of lamotrigine that might be causative for the observed hematologic effects. "(26)".As a result, the consequences of enzyme induction may take considerable time to be fully exhibited. The consequences of enzyme induction are an increased rate of metabolism, enhanced oral first-pass metabolism, and a reduced bioavailability.

All of this results in a decrease in the drug's plasma concentration. In contrast, in Drugs that are metabolized to an active or toxic metabolite, induction may be associated with an increased effect or increased toxicity. A well-documented and classic example of enzyme induction involves the drug rifampin and oral contraceptives (OCs). Rifampin is an antibiotic used in the treatment of tuberculosis and a potent metabolic inducer of CYP. Contraceptive failure is possible due to the altered metabolism of the OC. "(14)".Other common CYPInducers include phenytoin, carbamazepine, and the barbiturates "(15)".(Fig 5) enzyme enducer When drug-metabolizing enzymes are inhibited, there is an increase in the plasma concentration of the parent drug. This elevated concentration can lead to an exaggerated and prolonged pharmacological effect from the parent drug. Additionally, inhibition of metabolism can

result in a reduction in the formation of metabolites of the drug.This situation can potentially lead to drug-induced toxicity due to the increased levels of the parent drug in the body. Unlike enzyme induction, which typically takes time to develop, enzyme inhibition can occur rapidly and without warning.Some examples of potent inhibitors of CYP3A, a key drug-metabolizing enzyme, include:

- Antifungal agents ketoconazole and itraconazole
- Macrolide antibiotics such as erythromycin and clarithromycin (but not azithromycin) "(27)".

These drugs can interfere with the metabolism of other medications that are substrates of CYP3A, causing their plasma concentrations to rise and potentially resulting in adverse effects or toxicity. The metabolic inhibition may be reversible (competitive, metabolic-intermediate complex, non-competitive) or irreversible, and clinical effects are influenced by basic mechanisms "(5)".

- **Reversible inhibition: -**Competitive**-**The competitive inhibition occurs when inhibitor and substrate compete for the same binding site on the enzyme. In this type of interaction, the inhibition mechanism is direct and is rapidly reversible. However, recently we reported a case of an 85-year-old woman that developed visual hallucinations and psychomotor agitation during the treatment with venlafaxine and propafenone. "(28)".We postulated a DDI between venlafaxine and propafenone because venlafaxine is metabolized primarily by CYP2D6 and is a substrate of P-gp, while propafenone is a known substrate and inhibitor of both CYP2D6 and P-gp. Therefore, propafenone may be induced an increase of venlafaxine plasma concentrations with the development of hallucinations.

4.2. Metabolic-intermediate complexes

The production of metabolic-intermediate complexes is an unusual form of inhibition where the inhibitor binds only to the enzyme-substrate complex. The formation of a metabolic-intermediate complexes results from inhibitors that have an N-alkyl substituent. After the binding of inhibitor, the latter is oxidized by 3A4 and the resultant oxidized species of the inhibitor remains complexed with the reduced heme group of CYP3A4 forming a complex slowly reversible.Erythromycin is a well-known CYP3A4 inhibitors that use this mechanism of inhibition,whereas clarythromycin display reduced inhibitory effects with a good clinical efficacy."(16)".

Non-competitive: - In the non-competitive mechanism, the inhibitor and substrate do not compete for the same active site, because the presence of an allosteric site. Once a ligand binds the allosteric site the conformation of the active site changes, its ability to bind the substrate decreases and the product formation tails off. Many drugs are non-competitive inhibitors of CYP isoforms, as well as omeprazole and lansoprazole, and cimetidine. "(29,30)".The duration of this type of inhibition may be longer if new enzymes have to be synthesized after the inhibitor drug is discontinued.

Irreversible inhibition: -The metabolite resulting from the oxidation of the substrate by CYP3A4 becomes irreversible and covalently bound to 3A4, thus leading to a permanent inhibition of the enzyme. In the case of irreversible inhibition, the critical factor is represented by the total amount rather than the concentration of the inhibitor to which CYP isoenzyme is exposed. Lipophilic and large molecular size drugs are more likely to cause inhibition "(31)".Two characteristics make a drug susceptible to inhibitory interactions: one metabolite must account for >30-40% metabolism of a drug and that metabolic pathway is catalyzed by a single isoenzyme."(32)".

Excretion: -The kidney plays a crucial role in the excretion of drugs and other compounds from the body. While the liver is primarily responsible for metabolizing drugs, the kidney is the primary organ involved in eliminating these metabolites and other compounds.In addition to the kidneys, other sites of drug excretion include the liver (via bile), lungs (via exhalation), gastrointestinal tract (via feces), saliva, sweat, tears, and breast milk. Alterations in renal excretion can occur through various mechanisms:

- Changes in urinary pH: Alterations in urinary pH can affect the ionization of drugs, which in turn can impact their passive reabsorption in the renal tubules.
- Competition for the same transport system: Different drugs or endogenous substances may compete for the same transporters in the kidney, affecting the excretion of one or both substances.
- Changes in active tubular secretion: Some drugs are actively secreted into the renal tubules. Changes in this process can impact the elimination of these drugs.
- Changes in renal blood flow: Blood flow to the kidneys affects the filtration and subsequent excretion of substances.

All of these factors can contribute to alterations in drug excretion, potentially affecting the drug's concentration and efficacy in the body.

Acidification of the urine results in an increase in the rate of urinary excretion of weak bases Alterations in urine pH can influence the ionization of drugs. A more acidic urine environment favors the formation of the ionized, less lipid-soluble form of a drug. This can lead to a decrease in the amount of drug that is passively reabsorbed following filtration in the kidneys. On the other hand, renal excretion of weak acids is favored by more alkaline conditions. While alterations in urine pH typically do not play a major role in everyday undesired drug interactions, they can be utilized in the detoxification process to help eliminate drugs from the body in cases of drug overdose. Adjusting urine pH can impact the excretion rates of certain drugs, facilitating their removal from the body "(3)".The kidney is the organ responsible for the elimination of drugs and their metabolites. The interaction may occur for a mechanism of competition at the level of active tubular secretion, where two or more drugs use the same transport system. An example is given by NSAIDs that determine the appearance of toxic effects caused by methotrexate when the renal excretion of the anti-proliferative drug is blocked "(33)". Certainly. Probenecid is a well-known example of a drug that affects active tubular secretion of other drugs from the plasma into the renal tubular filtrate. It competes with other drugs for active transport sites in the proximal renal tubular epithelial cells. In the past, this interaction was used therapeutically. One classic application was combining penicillin with probenecid. The purpose of this combination was to increase the plasma levels of penicillin "(3)".By inhibiting its renal excretion with probenecid, the plasma concentration of penicillin would rise, thereby enhancing its therapeutic effects. This strategy was employed to prolong the action of penicillin and increase its efficacy in treating infections. "(3)".

5. Pharmacodynamic drug interaction

Pharmacodynamics is ‘what the drug does to the body’. These interactions occur between drugs with additive or opposing effects "(2)".Pharmacodynamic drug-drug interactions (DDIs) occur when the pharmacological effect of one drug is altered by that of another drug in a combination regimen. Quantitative evaluation of pharmacodynamic DDIs by employing modeling and simulation approaches is needed to identify and optimize safe and effective combination therapy regimens. DDIs often are classified as synergistic, additive, or antagonistic in nature, albeit these terms are frequently misused. The definition of additivity is that the overall effect caused by a drug combination is the sum of the pharmacological effects of each individual agent in the combination. **Synergy** occurs when the overall effect of the drug combination is greater than additive, and **antagonism** occurs when the drug combination effect is less than additive. Pharmacodynamic Drug DDIs can be beneficial and employed deliberately, or adverse and unintended. For example, in cancer chemotherapy regimens, folinic acid is used in combination with 5-fluorouracil (5-FU) to enhance 5-FU inhibition of thymidylate synthase, resulting in synergistic cytotoxicity against cancer cells. In a contrasting example, combining angiotensin converting enzyme (ACE) inhibitors with thiazide diuretics for hypertension may cause excessive diuresis and hypotension’s. This situation results partly from the fact that most PD DDI investigations are limited to high-throughput in vitro screening studies. They are less commonly tested in vivo, in animal models or clinical trials, in which complex, pathophysiological, systems-level interactions can occur. Pharmacodynamic interactions between drugs with additive effects may be intentional, for example when combining antihypertensives, or unintentional, for example serotonin syndrome caused by adding tramadol to a selective serotonin reuptake inhibitor (SSRI). Conversely, combining drugs with opposing effects can result in loss of drug effect, for example reduced bronchodilation by a beta2 agonist prescribed with a non-selective betablocker

5.1. Challenges in pharmacodynamic interaction

One of the primary challenges in the assessment of PD DDIs is a lack of knowledge of the detailed mechanism(s) of action and exposure-response relationships for each drug individually. For example, after more than a century of use, the exact mechanisms of action for aspirin are still being identified

5.2. The need for pharmacodynamic drug-drug interaction studies

Combination therapies are used widely in areas such as infectious disease, cancer, and cardiovascular diseases.One successful example is the highly active antiretroviral therapy (HAART) combination treatment that is often prescribed to patients with human immunodeficiency virus (HIV) or Acquired Immuno-Deficiency Syndrome. HAART regimens were designed to achieve substantial suppression of viral load by pharmacologically inhibiting virus entry, reverse transcription, integration, gene transcription, and replication, and these multiple objectives were achieved using different classes of drug. In this example, PD DDI studies can elucidate how the different drugs affect the virus-host interactions alone and in combination, demonstrate how mathematical models can be used to optimize current regimens6,7 and assist in the design of new combination therapies to decrease mortality from HIV infection "(34)".

5.3. Drug interactions before administration

Certain drugs react with each other and get inactivated if their solutions are mixed before administration. In combined oral or parenteral formulations, the manufacturers take care that such incompatibilities do not take place. In practice situations, these in vitro interactions occur when injectable drugs are mixed in the same syringe or infusion bottle. Some examples are:

- Penicillin G or ampicillin mixed with gentamicin or another aminoglycoside antibiotic
- Thiopentone sodium when mixed with succinylcholine or morphine
- Heparin when mixed with penicillin/genta micin/hydrocortisone
- IV. Noradrenaline when added to sodium bicarbonate solution.

In general, it is advisable to avoid mixing of any two or more parenteral drugs before injecting "(1)".

6. Selected drug interaction

6.1. Drug drug interactions

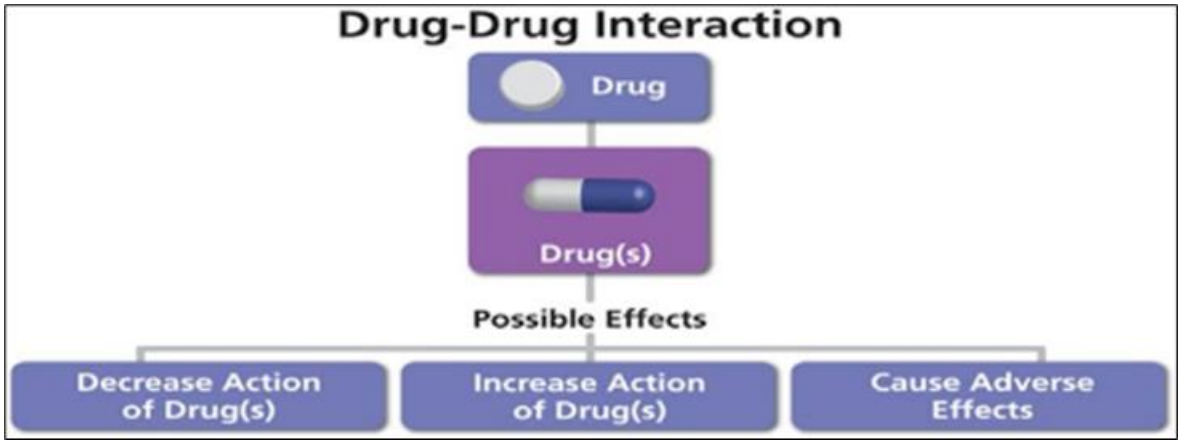

Figure 6 Drug drug interaction

Drug-drug interactions (DDIs) are a leading cause of adverse drug reactions (ADRs), especially among the elderly who often take multiple medications (poly-therapy). This complexity in treatment increases the likelihood of significant drug interactions, which can either decrease or enhance the effectiveness of treatment. These interactions are common and can lead to the development of adverse effects. (Acetophenon + warfarin)Acetaminophen is commonly used in the U.S. and is often recommended for patients on warfarin due to its lack of significant platelet inhibition or gastrointestinal bleeding. However, there is conflicting data regarding its interaction with warfarin, with some studies suggesting acetaminophen can increase warfarin's anticoagulant effect in a dose-dependent manner. Around 30% of patients on warfarin who consume about 2 g of acetaminophen daily may experience increased warfarin response. This interaction is more likely with daily doses exceeding 2 g for a week or more, while occasional doses are less likely to interact. Despite this, acetaminophen remains a valuable option for these patients as it does not affect platelet function or cause gastric irritation that can lead to bleeding, unlike aspirin and NSAIDs. It's important for clinicians to monitor coagulation parameters more closely, such as once or twice a week when initiating or discontinuing chronic acetaminophen therapy "(35)".The exact mechanism of this interaction is unknown, but it has been suggested that it may involve inhibition of CYP enzymes. Regardless, clinicians should be aware of this potential interaction and monitor patients closely.

6.1.1. Epinephrine + beta blocker

The adrenergic or sympathetic nervous system is regulated through alpha (α) and beta (β) receptors, which can have stimulatory or inhibitory effects depending on their type and location.In the heart, stimulation of beta-receptors leads to increased excitation, resulting in a positive effect on heart contraction strength (inotropy) and heart rate (chronotropy). This stimulation also enhances conduction speed in the sinoatrial node and reduces the refractory period of the heart muscl Overall, beta-receptor stimulation increases cardiac index, cardiac work, and oxygen consumption. These effects form the basis for the therapeutic uses of beta blockers, which are beta-receptor antagonists.The vascular system contains both alpha and beta receptors. Stimulation of beta-receptors causes blood vessel dilation (vasodilation), while stimulation of alpha-receptors leads to blood vessel constriction

(vasoconstriction).Epinephrine has both alpha and beta actions (Fig.6). Non-selective beta blockers block thevasodilating beta effect of epinephrine and shift the response to the alpha-mediated vasoconstriction, resulting in marked hypertension followed by reflexbradycardia (Fig. 7). This interaction has been recognized for years and has been the topic of numerous case .

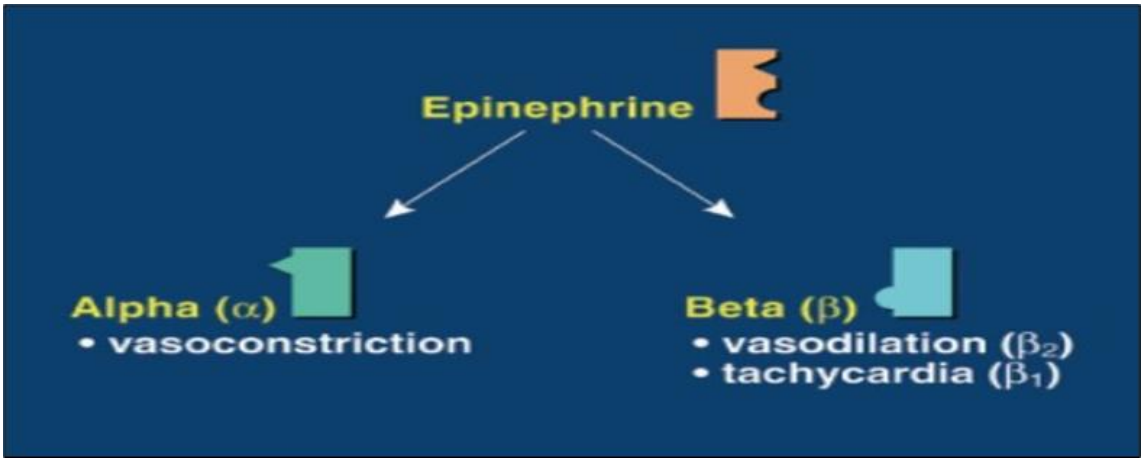

Figure 7 Epinephrine Receptor Action studies

The most significant report was by Foster and Aston, who cited six case studies involving plastic surgery. "(36)".No risk appears to beassociated with cardioselective beta blockers.a substance alters the activity of a drug

6.2. Food drug interaction

Numerous medications contain potent ingredients that interact with the body in diverse ways. Diet and lifestyle can exert considerable influence on how drugs behave. A drug interaction occurs when a substance alters the activity of a drug, resulting in increased or decreased effects, or even producing a new effect that neither substance causes independently.However, interactions may also exist between drugs and foods (drug-food interactions)Significant side effects of certain diets on medications involve changes in absorption caused by diets high in fat, protein, and fiber. Bioavailability, a crucial pharmacokinetic factor, is closely linked to the clinical effectiveness of many drugs. However, to assess the clinical significance of a food-drug interaction, it's necessary to quantify how food intake affects the drug's clinical effects.The critical interactions that often lead to treatment failure result from a notable decrease in drug bioavailability when taken with food. These interactions are commonly due to chelation with food components. Furthermore, the body's response to food intake, especially gastric acid secretion, can either decrease or increase the bioavailability of specific medications."(37)".

6.3. Tetracycline Interaction

Interactions with tetracycline reduce its bioavailability significantly: by 46–57% when consumed with food, by 50–65% with dairy products, and up to 85% with iron supplements. Tetracycline binds with polyvalent cations like iron, calcium, magnesium, and aluminum in the gut, preventing its absorption and leading to treatment ineffectiveness "(3)".(see Figure 9)

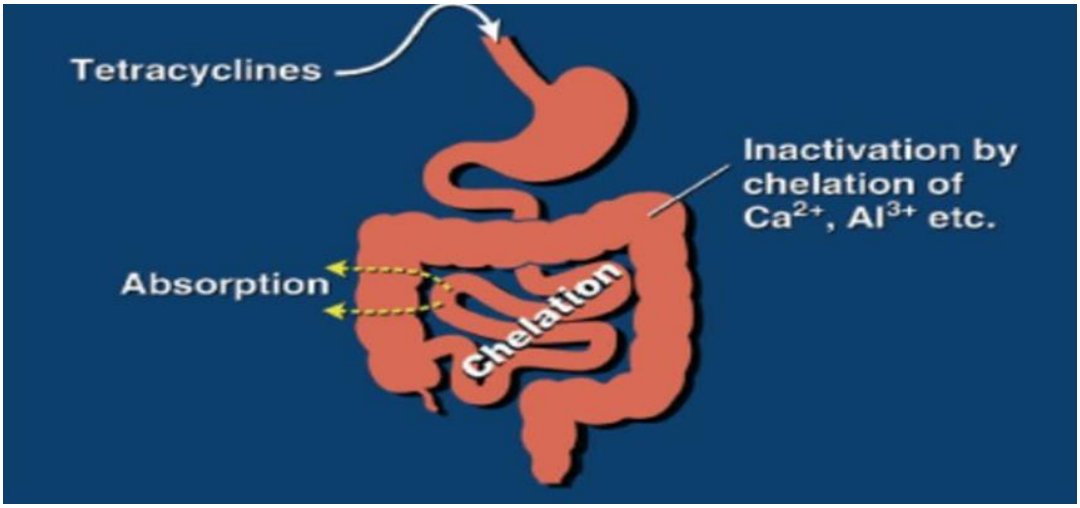

Figure 9 Tetracycline Chelation Interaction

6.4. Drug disease interaction

Drug interactions with diseases were infrequent except when patients had chronic kidney disease. It is suggested that guideline developers adopt a more systematic approach towards considering the possibility of drug-disease interactions. This approach could be based on epidemiological data about the common comorbidities associated with the disease the guideline is targeting, especially focusing on the prevalence of chronic kidney disease in the intended population. On the other hand, there were numerous potentially serious drug-drug interactions between recommended medications for different conditions. Given the significant number of these interactions, innovative and interactive methods are needed for creating and sharing guidelines.

This would enable clinicians and patients dealing with multiple health conditions to make well-informed decisions regarding drug choices.We categorized a drug as "first line" if it was suggested as a treatment for nearly all individuals with the condition (such as angiotensin-converting enzyme inhibitors for those with heart failure). Conversely, drugs recommended for only certain patients with the condition, under specific circumstances, were labeled as "second line" (like spironolactone for individuals with heart failure and significant symptoms despite first-line treatment) "(38)".

6.5. Drug allergy internation

Drug allergies include a range of immune-mediated hypersensitivity reactions with diverse mechanisms and clinical manifestations. These adverse drug reactions not only impact the quality of life for patients but can also result in delayed treatment, unnecessary medical tests, and, in severe cases, mortality.Due to the wide array of symptoms linked with the condition, diagnosing it can often be challenging. Therefore, it is advised to refer patients to an allergist who has expertise in identifying, diagnosing, and managing drug allergies if there is suspicion of a drug-induced allergic reaction. Diagnosis hinges on a thorough history, physical examination, and, in some cases, skin testing and graded challenges. In certain situations, procedures to induce drug tolerance may also be necessary. The most effective approach to managing drug allergy involves avoiding or stopping the problematic drug. When possible, substitute medications with different chemical structures should be considered. It's important to account for cross-reactivity among drugs when selecting alternative agents.Supplementary therapy for drug hypersensitivity reactions primarily focuses on supportive measures such as topical corticosteroids, oral antihistamines, and, in severe instances, systemic corticosteroids. In cases of anaphylaxis, injectable epinephrine is the preferred treatment. If a patient requires a specific drug to which they are allergic and there is no suitable alternative, procedures to induce drug tolerance may be contemplated to temporarily establish tolerance to the drug.Given the myriad of symptoms associated with the condition, diagnosis is often challenging. Therefore, referral to an allergist experienced in the identification, diagnosis and management of drug allergy is recommended if a drug-induced allergic reaction is suspected "(39)".

7. Conclusions

DDIs represent a common clinical problem during the management of patients treated with several drugs. However, may be underlined that only two drugs are able to induce the development of a DDI even if this clinical relevance is related to the pharmacology of each drug. In fact, a DDI will be able to induce a clinically relevant effect in presence of drugs with a low therapeutic index, a long half-life and a higher bound with plasma proteins.

Moreover, it is important to underline that the development of DDI is not a problem a class of drug but of a single drug and this problem could be under estimated considering the SPC only.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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