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PHARMACEUTICAL DRUG- DRUG INTERACTION: A REVIEW

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1. INTRODUCTION

Drug interaction is desirable or undesirable pharmacological effect of drugs interacting with other drugs, with endogenous physiologic chemical agents, with components of the diet, and with chemicals used in diagnostic tests. An interaction can either increase or decrease the effectiveness or the side effects of a drug, or it can create a new side effect not previously seen before.[1] Drug interactions may make the drug less effective, cause unexpected side effects or increase the action of a particular drug. Some drug interactions can even be harmful. Therefore, reading the label every time before using a nonprescription or prescription drug and taking the time to learn about drug interactions may be useful.[2] The probability of interactions increases with the number of drugs taken. The high rate of prescribed drugs in elderly patients (65-year-old patients take an average of 5 drugs) increases the likelihood of drug interactions and thus the risk that drugs itself can be the cause of hospitalization.[3]

Example: Propranolol and Asthma – propranolol is a beta blocker medication used to treat high blood pressure. Many healthcare providers avoid prescribing propranolol if someone has asthma. Propranolol can make the muscles that help you tighten, and can result in an asthma attack.

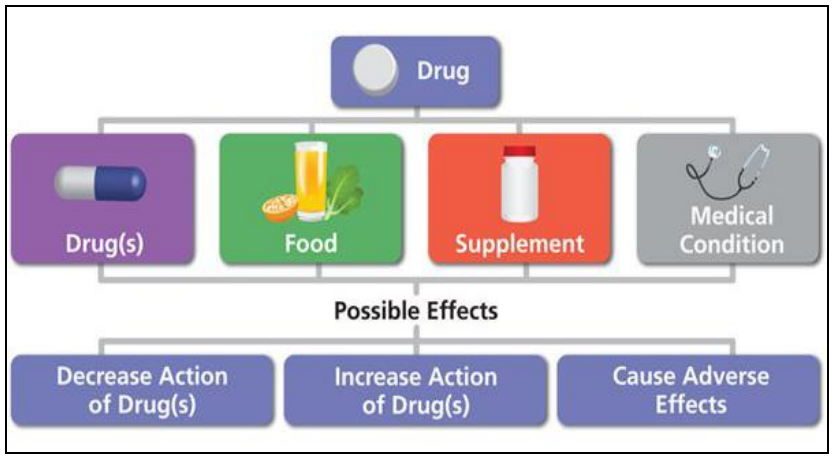

Fig. 1: Type of drug interaction.

1.2 Causes of drug interaction

There are many causes of drug interaction

1.2.1 Multiple drug therapy: Multi-drug therapy in this concept, we would propose that is defined as the specific use of two or more drugs for two or more chronic condition.

Example: Taking several antibiotics at a time is called as multiple drug therapy. Most of the medicines are given as pills. Antibiotic such as tetracyclin, ethambutol, isoniazid are used initially. Special treatment is provided to the people affected by HIV and TB, Pregnant women with TB.

Fig. 2: Multiple drug therapy.

1.2.2 Multiple prescriber: It can be defined as if we go to different – different doctors for the treatment of disease and the prescriber don't know about your previous medical history, so the prescriber prescribe new drug for the treatment of your disease, so these drug may interact with previous drug which is prescribed by another prescriber, so the multiple prescriber also cause the drug interaction in our body.

Fig. 3: Multiple prescriber.

1.2.3 Multiple diseases: Multiple diseases defined as more than two illnesses or diseases occurring in the same person at the same time.

Example: some beta-blockers taken for heart disease or high blood pressure can worsen asthma or make it hard for people with diabetes to tell when their blood sugar is too low.[4]

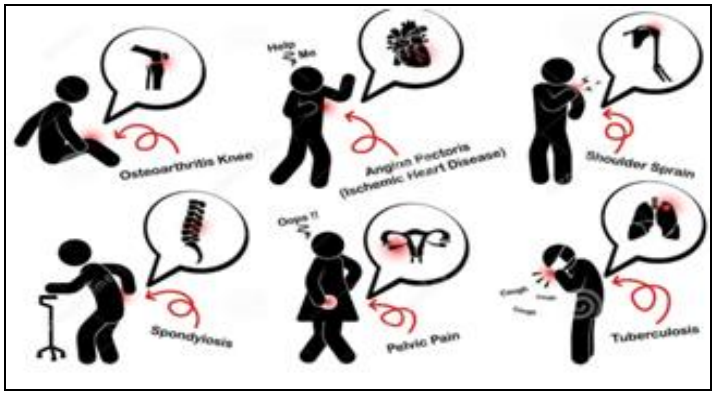

Fig. 4: Multiple diseases.

1.3 Types of drug interaction

1.3.1 Drug – drug interaction
1.3.2 Drug – food interaction
1.3.3 Drug – disease interaction

1.3.1 Drug-drug interaction

Drug-drug interactions (DDIs) occur when the effects of a drug are changed by the presence of another drug, resulting in synergistic, additive or antagonistic

outcomes and are an important cause of preventable adverse drug events.[5]

Drug-drug interaction (DDI) is one of the kinds of drug related problems in which effects of one drug can be altered by the co-administration of another drug. DDIs are termed as pharmacological and clinical outcomes resulted from simultaneous use of different combinations of drugs as compared to their use alone. These DDIs could result in serious life threatening conditions in a desire to alter the therapeutic end point of drugs. DDI is said to account for a number of severe ADR resulting in hospitalizations and emergency department visits.[6] Many adverse events can be prevented by identifying potential drug interactions. However, certain conditions such as multiple disorders, chronic diseases and polypharmacy may increase the risk of drug-drug interaction.[7] Clinical efficiency as well as prevalence of adverse drug reaction is directly proportional to the development of drug - drug interaction, the more drug interact with each other, the more likelihood of adverse drug reactions and hence clinical effectiveness of medication will also be affected.[8]

Example: mixing a drug you take to help you sleep (a sedative) and a drug you take for allergies (an antihistamine) can slow your reactions and make a car or operating machinery dangerous.

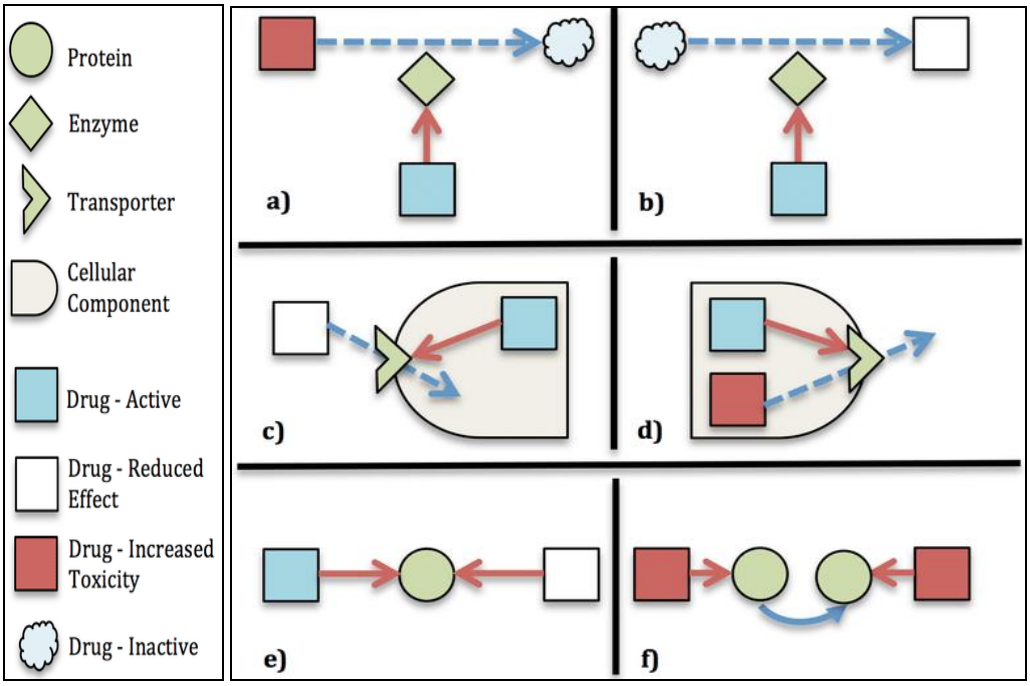

Fig. 5: Potential mechanism of drug interaction.

1.3.2 Drug- food interaction

A drug-food interaction happens when the food affects the ingredients in a medicine which the patient is taking affecting the efficacy of medicine being administered. The relationship and interaction between food, the nutrients they contain and drug are gaining recognition in the health care and medical fields. Certain food and specific nutrients in foods, if ingested concurrently with some drugs, may affect the overall bioavailability, pharmacokinetics, pharmacodynamics and therapeutic efficacy of the medications. Furthermore, the therapeutic efficacy of many drugs depends on the nutritional status of the individual.[9] In other words, the presence or absence of some nutrients in the gastrointestinal tract or in the body's physiological system, such as in the blood, can enhance or impair the rate of drug absorption and metabolism. Drug- food interaction can happen with both prescription and over-the-counter drug, including antacid, vitamins and iron pills. Food containing active substance that interacts against certain medications can produce unexpected or adverse effects[10]. Pharmacist can give the information of such interaction to the patients.

Food: Like food, drugs taken by mouth must be absorbed through the lining of the stomach or the small intestine. Consequently, the presence of food in the digestive tract may reduce the absorption of a drug. Often, such interactions can be avoided by taking the drug one hour before or two hours after eating. Dietary fiber also affects drug absorption. Pectin and other soluble fibers slow down the absorption of acetaminophen, a popular painkiller. Bran and other insoluble fibers have a similar effect on digoxin, a major heart medication. Certain vitamins and minerals impact on medications too. Large amounts of broccoli, spinach and other green leafy vegetables high in vitamin K, which promotes the formation of blood clots, can counteract the effects of heparin, warfarin and other drugs given to prevent clotting.[11]

Example

- Taking some medicines at the same time with food may affect the absorption of the medicine; the food may delay or decrease the absorption of the medicines. This is why some medicines should be taken on an empty stomach. On the other hand, some medicines are easier to tolerate when taken with food. It is always advised to ask the doctor or pharmacist.
- Mixing alcohol with some drugs may cause you to feel tired or slow your reactions.

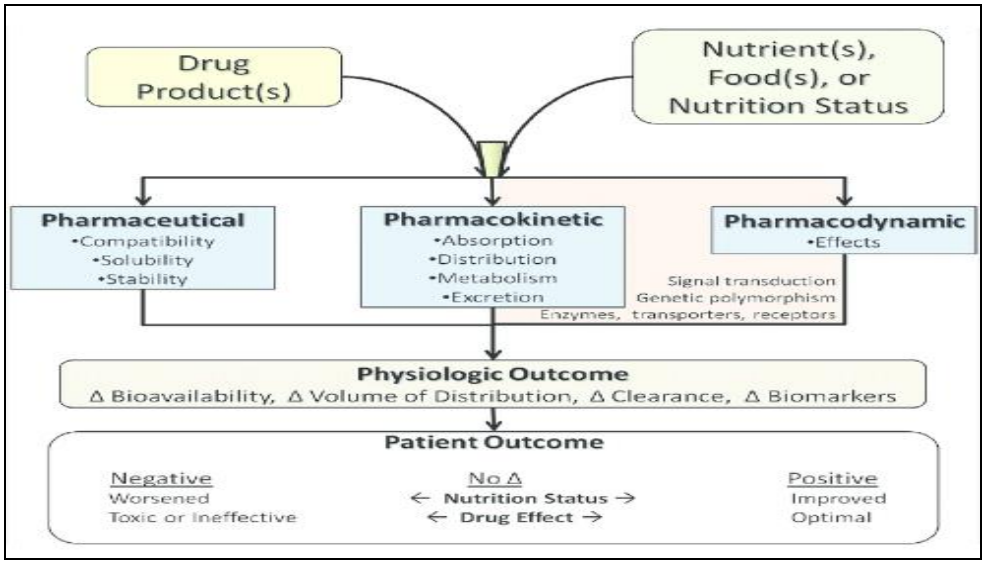

Fig. 6: Working model of drug-food interaction.

1.3.3 Drug - disease interaction

Drug disease interaction may occur when an existing medical condition makes certain drugs potentially harmful.

A prescribing cascade occurs when the adverse effect of a drug is misinterpreted as a symptom or sign of a new disorder and a new drug is prescribed to treat it. The new, unnecessary drug may cause additional adverse effects, which may then be misinterpreted as yet, another disorder and treated unnecessarily, and so on.

Many drugs have adverse effects that resemble symptoms of disorders common in older adults or changes due to aging [12].

Example: if you have high blood pressure you could experience an unwanted reaction if you take a nasal decongestant.

These are the following conditions

Antipsychotics may cause symptoms that resemble Parkinson disease. In older adults, these symptoms may be diagnosed as Parkinson disease and treated with dopaminergic drugs, possibly leading to adverse effects from the antiparkinson drugs (*eg.*, orthostatic hypotension, delirium, hallucinations, nausea).[13]

Cholinesterase inhibitors (*eg.*, donepezil, rivastigmine, galantamine) may be prescribed for patients with dementia. These drugs may cause diarrhea or urinary frequency or urge incontinence. Patients may then be prescribed an anticholinergic drug (*eg.*, oxybutynin) to treat the new symptoms. Thus, an unnecessary drug is added, increasing the risk of adverse drug effects and drug-drug interactions. A better strategy is to reduce the dose of the cholinesterase inhibitor or consider a different treatment for dementia (*eg.*, memantine) with a different mechanism of action.[14]

Calcium channel blockers: (*eg.*, amlodipine, nifedipine, felodipine) may be prescribed for patients with hypertension. These drugs may treat the hypertension appropriately, but they may also cause peripheral edema. Patients may then be prescribed diuretic therapy (*eg.*, furosemide), which may then cause hypokalemia necessitating potassium supplementation. A better strategy is to reduce the dose or discontinue the calcium channel blocker in favor of other antihypertensive drugs, such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers.[15]

1.4 Mechanism of drug interaction

1.4.1 Pharmacokinetic drug interaction
1.4.2 Pharmacodynamic drug interaction
1.4.3 Pharmaceutical drug interaction

1.4.1 Pharmacokinetic drug interaction

Pharmacokinetics is defined as what the body does to a drug, or more formally, the movement of drugs through the body including the processes of absorption, distribution, metabolism, and excretion (ADME). The pharmacokinetics of a drug is described in terms of drug concentration in the blood or plasma vs. time. The drug must achieve adequate concentration at the site of

activity (cell receptor site) to exert a pharmacologic effect, which is dependent on ADME. Think of pharmacokinetics as the time course of the drug concentration from a particular dosage regimen. Pharmacokinetics can tell us how much of a drug to give and how often it must be given to reach the target drug concentration that causes the desired pharmacological effect. Pharmacokinetic drug interactions can occur at any point in ADME.[16]

1.4.1.1 Absorption

Gastro-intestinal absorption

Absorption is the process by which drug molecules cross biological membranes from the site of administration into the plasma. When anaesthetic drugs are administered IV. Absorption problems are largely by passed with the use of volatile anaesthetics, the absorption might be influenced by ventilation–perfusion ratios or membrane pathology, but also by ventilator settings, as this is mainly dependent on gradients between alveoli and pulmonary capillaries. After anaesthesia with halothane and diazepam, peak plasma paracetamol concentrations of paracetamol administered 1 h after surgery were significantly delayed and decreased, compared with conditions without anaesthesia, as a result of delay in gastric emptying and therefore slower absorption[17].The complexity of the gastro-intestinal tract and the effects of several drugs with functional activity in the digestive system represent favorable conditions for the emergency of DDI that may alter the drug bioavailability.

Several factors may influence the absorption of a drug through the gastrointestinal mucosa. The first factor is the change in gastric pH. The majority of drugs orally administered require, to be dissolved and absorbed, a gastric pH between 2.5 and 3. Therefore, drugs able to increase gastric pH (*i.e*., antacids, anticholinergics, proton pump inhibitors [PPI] or H_2-antagonists) can change the kinetics of other co-administered drugs. In fact, H_2 antagonists (*e.g*., ranitidine), antacids (*e.g*., aluminium hydroxide and sodium bicarbonate) and PPI (*e.g*., omeprazole, esomeprazole, pantoprazole) that increase the gastric pH lead to a decrease in cefpodoxime bioavailability, but on the other hand, facilitate the absorption of beta-blockers and tolbutamide. Moreover, antifungal agents (*e.g*., ketoconazole or itraconazole), requires an acidic environment for being properly dissolved, therefore, their co-administration with drugs able to increase gastric pH, may cause a decrease in both dissolution and absorption of antifungal drugs.

Therefore, antacid or anti-cholinergics, or PPI might be administered at least 2 h after the administration of antifungal agents. Similarly, the administration of drugs able to increase the gastric pH with ampicillin, atazanavir, clopidogrel, diazepam, methotrexate, vitamin B12, paroxetine and raltegravir are not recommended. In contrast, the ingestion of drugs that cause a decrease in gastric pH (*e.g*., pentagastrin) may have an opposite effect. It is worth noting that severity of DDIs caused by alteration of gastric pH mainly depends on pharmacodynamics characteristics of the involved drug, in terms of narrow therapeutic range.

Another factor that modifies the drug absorption is the formation of complexes. In this case, tetracyclines (*e.g*., doxycycline or minocycline) in the digestive tract can combine with metal ions (*e.g*., calcium, magnesium, aluminum, iron) to form complexes. The incidence of Potential drug–drug interactions in cardiac patients in a tertiary care hospital. Consequently certain drugs (*e.g*., antacids, preparations containing magnesium salts, aluminum and calcium preparations containing iron) can significantly reduce the tetracyclines absorption. Analogously; antacids reduce the absorption of fluoroquinolones (*e.g*., ciprofloxacin), penicillamines and tetracyclines, because the metal ions form complexes with the drug. In agreement, was observed that antacids and fluoroquinolones should be administered at least 2 h apart or more. Cholestyramine and colestipol bind bile acids and prevent their absorption in the digestive tract, but they can also bind other drugs, especially acidic drugs (*e.g*., warfarin, acetyl salicylic acid, sulfonamides, phenytoin, and furosemide). Therefore, the interval between the administration of cholestyramine or colestipol and other drugs may be as long as possible (preferably 4 h).

Motility disorders represent the third factor involved in absorption DDIs. Drugs able to increase the gastric transit (*e.g*., metoclopramide, cisapride or cathartic) can reduce the time of contact between drug and mucosal area of absorption inducing a decrease of drug absorption (*e.g*., controlled-release preparations or entero-protected drugs).[18]

Example: metoclopramide, may accelerate gastric emptying, hence decreasing the absorption of digoxin and theophylline whereas it can accelerate the absorption of alcohol, acetylsalicylic acid, acetaminophen, tetracycline and levodopa. Finally, iron can inhibits the absorption of levodopa and methyldopa.

1.4.1.2 Distribution

Usually, drugs are transported through a binding to plasma and tissues proteins. Of the many plasma proteins interacting with drugs, the most important are albumin, α1- acid glycoprotein, and lipoproteins. Acidic drugs are usually bound more extensively to albumin, while basic drugs are usually bound more extensively to α1-acid glycoprotein, lipoproteins, or both. Only unbound drug is available for passive diffusion to extra vascular or tissue sites and typically determines drug concentration at the active site and thus its efficacy. Albumin represents the most prominent protein in plasma, it is synthesized in the liver and distributed in both plasma and extracellular fluids of skin, muscles and various tissues.

Intestinal fluid albumin concentration is about 60% of that in the plasma. Since albumin has five binding sites (*i.e.*, for warfarin, benzodiazepines, digoxin, bilirubin and tomoxifen), the main characterized are the site I and II. Site I, also known as the warfarin binding site, is formed by a pocket in subdomain IIA, while site II located in subdomain IIIA is known as the benzodiazepine binding site. Ibuprofen and diazepam are selective drug probes for site II. As the free molecules interact with their molecular targets and are metabolized, other molecules come into solution to reach the site of action.

The degree of plasma protein binding, expressed by the ratio of bound drug concentration/free drug concentration, varies greatly among drugs, possibly reaching very high values, especially when it is greater than 0.9, otherwise it is considered to be low (90%), reduced volume of distribution, narrow therapeutic index, and it is characterized by a faster onset of the effect. A typical pharmacological displacement can be observed when warfarin and diclofenac are co-administered. Warfarin and diclofenac have the same affinity for albumin, therefore the administration of diclofenac to a patient treated chronically with warfarin results in displacement of latter from its binding site. The increase in plasma concentration of free warfarin causes the development of serious hemorrhagic reactions.[19]

1.4.1.3 Metabolism

The CYP enzyme family plays a dominant role in the biotransformation of a wide number of drugs. In man, there are about 30 CYP isoforms, which are responsible for drug metabolism and these belong to families 1-4, but only 6 out of 30 isoforms belonging to families CYP1, 2 and 3 (*i.e.*, CYP1A2, 3A4, 2C9, 2C19, 2D6 and 2E1) are mainly involved in the hepatic drug metabolism.[25, 26, 27, 28, 29] The broad range of drugs that undergo CYP mediated oxidative biotransformation is responsible for the large number of clinically significant drug interactions during multiple drug therapy. Many DDIs are related to the inhibition or induction of CYP enzymes.[20]

Inhibition

Inhibition-based DDIs constitute the major proportion of clinically relevant DDIs. In this process enzyme activity is reduced due to direct interaction with a drug, usually begins with the first dose of the inhibitor, while the extinction of inhibition is related to the drug half-lives. The metabolic inhibition may be reversible (competitive, metabolic-intermediate complex, non-competitive) or irreversible, and clinical effects are influenced by basic mechanisms.[21]

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. The drugs are converted through multiple CYP dependent steps to nitrosoderivatives that bind with high affinity to the reduced form of CYP enzymes. Thus CYP enzymes are unavailable for further oxidation and synthesis of new enzymes is, therefore, the only means by, which activity can be restored and this may take several days. It depends on the substrate-versus-inhibitor binding constant ratio, and on the relative concentrations of each species. Some of the inhibitors of CYP3A4 that act by this mechanism of inhibition include azole antifungal agents, some HIV protease inhibitors such as nelfinavirmesylate, and antihypertensive such as diltiazem.[22]

Metabolic-intermediate complexes

The production of metabolic-intermediate complexes are an unusual form of inhibition where the inhibitor binds only to the enzyme-substrate complex. The formation of a metabolic-intermediate complex results from inhibitors that have a Nalkyl 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 well-known CYP3A4 inhibitors that use this mechanism of inhibition, whereas clarythromycin display reduced inhibitory effects with a good clinical efficacy.[23]

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. The duration of this type of inhibition may be longer if new enzymes have to be synthesized after the inhibitor drug is discontinued.[24]

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. 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. Inhibitor will decrease the metabolism of the substrate and generally lead to increased drug effect or toxicity of the substrate. If the drug is a pro drug the effect is decreased.[25]

Metabolic induction

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. The most common mechanism is transcriptional activation leading to increased synthesis of more CYP enzyme proteins. The effect of induction is simply to increase the amount of P450 present and speed up the oxidation and clearance of a drug.[26]

1.4.1.4 Excretion

The organs and vehicles deputy at the drug excretion (elimination) are kidneys, liver, lungs, faeces, sweat, saliva, milk. The excretion through saliva, sweat and lungs (for volatile drugs) and milk has little quantitative significance, but the milk is important when the drugs can reach the baby during lactation. Drugs are excreted mainly through: Renal tubular excretion (glomerular filtration, tubular reabsorption and active- tubular secretion) biliary excretion. 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. It was also demonstrated that amoxicillin decreased the renal clearance of methotrexate. Probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, increases of 2.5 times the area under the AUC of oseltamivir. However, this competition between drugs can be exploited for therapeutic purposes.[27]

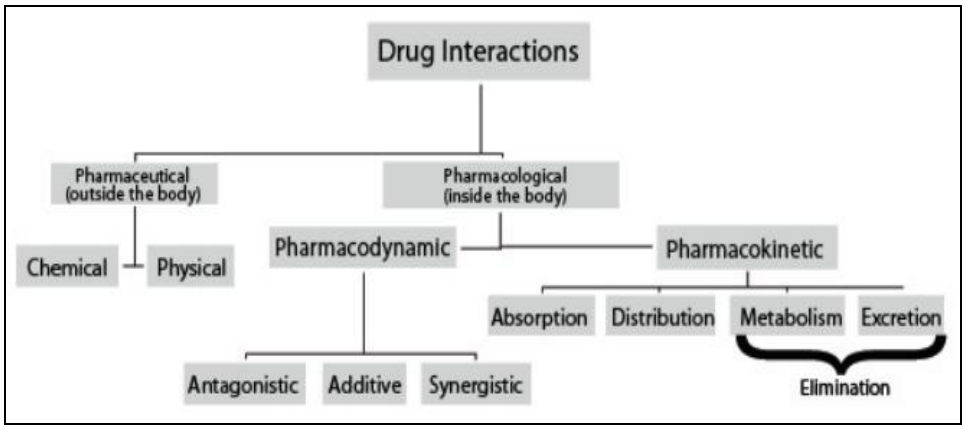

Fig. 7: Classification of drug interaction.

1.4.2 Pharmacodynamic drug–drug interactions

Occur when interacting drugs have either additive effects, in which case the overall effect is increased, or opposing effects, in which case the overall effect is decreased or even 'cancelled out'. Pharmacodynamics is 'what the drug does to the body.[28] These interactions occur between drugs with additive or opposing effects. The brain is the organ most commonly compromised by pharmacodynamic interactions. Pharmacodynamic interactions between drugs with additive effects may be intentional, for example when combining anti-hypertensives, 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 beta 2 agonist prescribed with a non-selective beta blocker.[29]

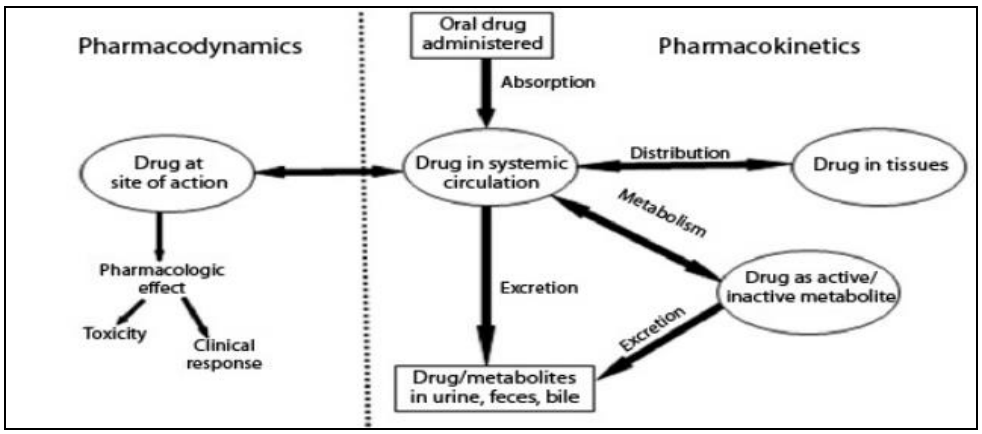

Fig. 8: Pharmacokinetic and Pharmacodynamic drug activity.

Pharmacodynamic interaction can be beneficial in that an improved therapeutic response may occur or be detrimental in that toxicity may be heightened. Also, therapeutic activity and toxic effects may occur simultaneously in opposite directions, resulting in a balance between positive and negative responses. Beneficial pharmacodynamic drug interaction abound in infectious disease therapy because of the many of drug combination used to treat infections.[30]

Pharmacodynamic drug interaction can occur as

1.4.2.1 Synergism

When the therapeutic or toxic effects of two drugs are greater than the sum effects of individual drugs.

Example: the combination of sulfamethoxazole and trimethoprim is more effective as compare to individual which are used as antimicrobial agent.[31]

1.4.2.2 Antagonism

An interaction between two or more drugs that have opposite effects on the body. Drug antagonism may block or reduce the effectiveness of one or more drugs.

Example: Acetylcholine and nor-adrenaline have opposing effects on heart rate.[32]

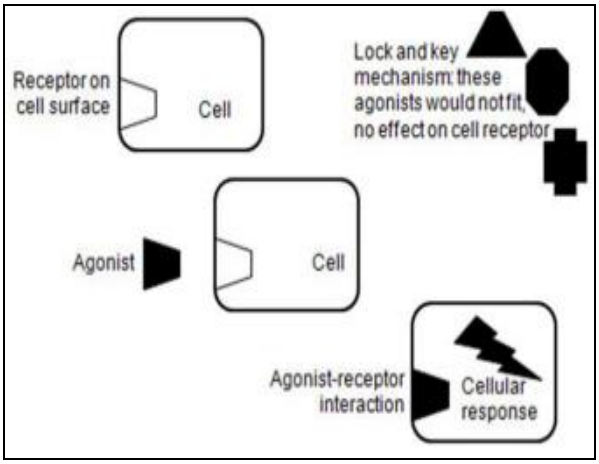

Fig. 9: Drug (agonist)-receptor interaction.

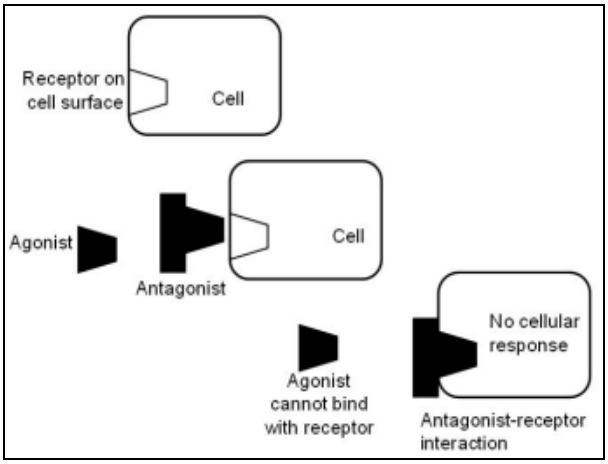

Fig. 10: Drug (antagonist)-receptor interaction.

1.4.3 Pharmaceutical drug–drug interactions

Occur when the formulation of one drug is altered by another before it is administered. Pharmaceutical drug interaction can be divided into chemical and physical reactions.

1.4.3.1 Chemical Drug interaction

Pharmaceutical drug interactions can be divided in to chemical and physical reactions. An example of a chemical reaction is the incompatibility of potassium phosphate and calcium chloride in total parenteral nutrition preparations, also known as hyperalimentation. The two drugs may interact to form calcium phosphate, which will result in a precipitate in the intravenous (IV) fluid bag. Persistent seizures (status epilepticus) is a life threatening condition that requires medication to stop the seizures as soon as possible. Two commonly used anticonvulsant drugs, phenytoin (Dilantin) and lorazepam (Ativan), become ineffective if mixed together in the same IV bag or syringe [33 34, 35]

1.4.3.2 Physical drug interaction

Physically altering a drug formulation such as by crushing a sustained-release tablet could result in the drug being released more quickly and/or in a larger amount. Alcohol or food given with some sustained release products may cause similar problems. Another example of a physical reaction includes the thyroid drug levothyroxine sticking to IV tubing and bags.[14] One drug can alter the formulation of another drug, such as the combination of diazepam (Valium) with the emulsion propofol (Diprivan). Diazepam destabilizes the propofol emulsion, causing it to "oil out" and making it dangerous to administer intravenously.[15] Environmental conditions can adversely affect drugs. Light can cause some drugs to degrade and become less effective. This is why medicine bottles are usually amber or opaque. Humidity can have a similar effect on drugs. Other environmental conditions can affect drug absorption.

Example: heating pads can increase the release of the narcotic fentanyl from transdermal patches.[36,37,38,39]

Fig.4: During collection of patient drug interaction details

Table 1: Case study on drug-drug interaction during the treatment at district hospital Etawah, Uttar Pradesh, India.

Sr. no.	Patient's name	Age	Sex	Disease condition	Prescribe drug	Drug-drug interaction	Symptoms observed
1.	Mr. Ramsingh	39	Male	High blood pressure	Propranolol	Propranolol + Nasal decongestant (pseudoephedrine)	Breathing problem Blurry vision Bloody nose
2.	Mr. Ramnaresh	46	Male	Glaucoma	Latanoprost (xalatan) eye drop	Latanoprost + Diphenhydramine	Change eye color Redness in eye
3.	Mr. Brajesh	67	Male	Diabetes	Metformin	Metformin + digoxin	Weakness. Muscle pain Shortness of breath
4.	Mrs. Sunita Devi	53	Female	Liver pain	Gastro resistant aspirin	Aspirin + acetaminophen	Liver damage Vomiting
5.	Mr. Prabhudayal	73	Male	Asthma	Salbutamol	Salbutamol + amiodarone	Damage blood vessels Tiredness

2. CONCLUSION

The physicians should be aware of interactions among those drugs while prescribing for patients and thorough monitoring should be required for the patient safety by the implementation of admonitory guidelines and computer-based screening, which might help to prevent potentially harmful drug interactions.

The study are highlighted the need for future studies to be conducted in order to improve the prescriber's awareness on drug-drug interaction and their management improving the clinical outcomes. Clinicians should consult drug-drug interaction information, evaluate it and consider its relevance for their patient's. For new drugs or when information is in consistent or absent, it may be necessary to refer to multiple interaction resources or seek expert advice, for example from a medicines information pharmacist.

With the increasing appreciation of known and potentially important drug interactions covering the broad spectrum of infectious diseases, the need for clarification othe clinical importance of these interactions has become imperative. An awareness of the role of pharmacokinetics, pharmacodynamics, and factors that alter these processes and insight into differentiating clinical and statistically significant effects are important variables in the clinician's process of decision making. This volume is intended to provide an in-depth review of drug interactions related to a number of topics in infectious diseases. An emphasis on the clinical approach with specific examples and cases will guide the reader in developing skills for identifying drug interactions and problem drugs as well as strategies for circumventing of drug interactions.

Drug-drug interaction represents 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 drug-drug interaction even if this clinical relevance is related to the pharmacology of each drug. In fact, a drug- drug interaction will be able to induce a clinically relevant effect in presence of drugs with low therapeutic index, a long half life and a higher bound with plasma proteins.

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