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Review Article

AN OUTLOOK ON THE MECHANISMS OF DRUG INTERACTIONS WITH OTHER DRUGS, FRUITS, HERBS AND THEIR PREVENTIVE MEASURES

ASHA K RAJAN[1], KOUSALYA K[2]*, SENTHIL NATHAN B[3], VALENTINA P[4]

[1]Department of Pharmacy Practice, Jaya College of Paramedical Sciences, College of Pharmacy, Thiruninravur, Chennai, Tamil Nadu, India. [2]Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels University, Chennai, Tamil Nadu, India. [3]Department of Pharmaceutics, Jaya College of Paramedical Sciences, College of Pharmacy, Thiruninravur, Chennai, Tamil Nadu, India. [4]Department of Pharmaceutical Chemistry, Jaya College of Paramedical Sciences, College of Pharmacy, Thiruninravur, Chennai, Tamil Nadu, India. Email: happykousi@gmail.com

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ABSTRACT

Drugs taken by a person are affected by a number of ways. A number of interactions are known to affect the drugs, change its efficacy or result in toxicity. Habits of a common person could also cause such interactions. Most of the people have habits of smoking, consumption of alcohol and taking dietary supplements without the advice of their physicians. Some drug interactions such as those between drug-herbs and drug-citrus fruit would bring us shock; even small fruit could sometimes bring adverse drug reactions to occur in our body. Due to drug interactions, there would sometimes be an increase or decrease in the efficacy of a drug. Being a pharmacist, it would be their ultimate role to check at a person's hygienic record, looking and gathering information of the past recorded drugs, dietary supplements, hereditary diseases, etc. They would have to gather information about the recently releasing drugs and know complete information on the reactions which occur on their administration. Knowledge to people about herbal and food-drug interactions is very less. They take them to be natural and do not care about its consequences. However, this interaction depends on the amount and the potency of pharmacologically active ingredient present in the compounds. These herbal drugs are known to contain a varying number of phytochemicals which may cause a change to the transporters, enzymatic systems, causing failure of the therapeutic effect of the drug interactions. The elimination of some particular drugs is also affected due to these interactions. As a result of this interaction, a number of drugs which had taken birth had quickly been removed from the US markets. Thus, the ways for a person to avoid these interactions can only be the above mentioned advices given by the health practitioners, not to administer drugs by self-medication methods, taking a note of all the additional supplements taken by a patient to his physician, so that there is a clear picture about the interactions at their initial stage. (1) There are various drug interactions with a number of factors. (2) Unless there is clear knowledge about the pathway of drug elimination, drug interaction stands to be very difficult to be avoided.

Keywords: Drug-food interactions, Pharmacokinetic, Pharmacodynamic, Drug-drug interactions.

INTRODUCTION

In general patients being hospitalized, or even after a normal visit, sometimes a checkup from a physician, receive two or more drugs, most of the times elderly patients may even have situations of taking eight or even more drugs concurrently. Multiple-drug therapy is preferred in the society due to many reasons. The treatment of diseases, such as cancer, cardiovascular diseases, infections, requires the action of multiple-drug therapy. Combinations of more than two drugs are found to be active in the treatment of these diseases.

Another reason would be the condition of the patients sometimes suffering from concurrent diseases. In such cases, number of drugs is to be administered at the same time, leading to increase in drug combinations. In some other cases, people would medicate themselves with over-the-counter medicines and herbal preparations. All these different cases during drug therapy would lead to drug interaction.

The alteration of the pharmacokinetics or pharmacodynamics of one drug by that of another would lead to the occurrence of drug interactions. Sometimes, herbal preparations and some food products would also alter the pharmacokinetics and pharmacodynamics of the drugs. For example, grape juice inhibits gut wall CYP3A, and there is the induction of this enzyme by St. John's Wort. Although being therapeutically important, food and drug interactions are not considered much [1].

There is a limitless potential for interactions of these drugs among themselves within the body causing variability in drug response. The concentration of the interacting drug is the criteria on which the drugs are graded in nature. A therapeutic drug interaction occurs when the risk of interaction increases with an increase in the number of drugs administered by the patients. Sometimes there is an exaggerated response of the affected drug due to this interaction. Due to the drug being either an antagonist, or it reduces bioavailability, reduced activity can take place. There may even be the removal of the drug from the market due to the interaction being much more severe than expected. Examples of such cases are antihistamines like terfenadine, astemizole, mibefradil and drugs used to treat heartburn such as a statin, cerivastatin or cisapride. Until there are cases of fatal occurred, there would not be the removal of these drugs from the market.

Many reasons could be quoted for a pharmacodynamic interaction to occur. Sometimes the interacting drug complements the action of another drug. Like the thiazide diuretics and a β blocker, where each of them act by a different mechanism to lower the blood pressure on the same receptor site as the other drug, the interacting drug could act as agonist or antagonist, may be as an additive or a synergistic. One of the examples of the mutual sedative effects of pharmacodynaic interactions is diphenhydramine and alcohol. Under pharmacokinetic interactions, there is an inhibition of midazolam which mediates its metabolism on intestinal CYP3A4 by saquinavir [1].

EXAMPLES OF COMBINATION OF PRODUCTS INSTALLING PHARMACOKINETIC ACTIVITY

Indicated for systemic infection, a combination of amoxicillin and clavulanate is found to be effective. β-lactamases that destroy this antibiotic (amoxicillin) are locally produced by some microorganisms. Hence these organisms are resistant to amoxicillin, this resistance is being overcome by clavulanate, which inhibits β-lactamases.

Thus, the antibiotic exposure locally is increased. A combination of imipenem and cilastatin is prescribed for urinary tract infection. Renal dehydropeptidase is responsible for the metabolism of imipenem in the kidney. This is inhibited by cilastatin which increases the concentration of the urinary tract of this antibiotic.

CLASSIFICATION

The alteration of the pharmacokinetics or pharmacodynamics is the criteria on which interaction is classified. An increase or decrease in drug response also serves to be a mode of classifying drug interactions. Interaction simply implies a mutual effect. The interaction effect between two drugs A and is denoted as A ↔ B. An example toward this effect could be put forward as under. The absorption of the diuretic furosemide is decreased by phenobarbital, but the diuresis produced by furosemide increases the renal clearance of phenobarbital. Thus, there is a bidirectional interaction denoted as A ↔ B.

There is not always a mutual interaction between two drugs. The method usually followed in therapy is unidirectional. For example, theophylline is inhibited by the antibiotic enoxacin, but this antibiotic does not suffer such an effect. Thus, the interaction is unidirectional being denoted as A → B [1].

INHIBITION

There is a complete increase in time in the plasma concentration of a drug by the inhibition when the pathway is the main route of eliminating the inhibited drug. It takes time to achieve the 10-fold increase in the concentration of the inhibited drugs. It may take even more, as it takes more time for the production of the maximum degree of inhibition, for the inhibitor on its regimen and even because the degree of inhibition rises as the concentration of the inhibitors rises to its plateau in time. There is an increase in the half-life of the inhibited drug. Thus, this prolongs the time in achieving the new plateau of the drug inhibited. Perhaps several weeks after the addition of the drug causing the interaction to the patient's regimen and there would not be an association of the cause of the toxicity with the case by the patient or the prescriber. There is a complete rise in the inhibited drug concentration and it is potentially harmful and dangerous. After the addition of the inhibitor, the toxicity in higher concentrations may not become apparent and be like mystery.

A final point to be noted in this case is that patients may receive a number of weak or moderate competitive inhibitors of an enzyme. On the administration of each of them individually, the AUC changes of the drug inhibited are too small for a dose adjustment to be warranted but on the administration of multiple inhibitors consecutively there is a sufficiently great inhibition of the enzyme. Then, there is a warrant of classification of the inhibitors combination as "strong inhibitors," sometimes reducing the dose of the victim drug or accepting alternatives.

A drug interaction includes both object drug and a precipitant. The various forms of drug interactions may be [2]:

- Drug-disease interaction: A drug worsens the condition of a disease
- Drug-laboratory test interaction: The presence of a drug alters laboratory test results
- Drug-chemical interaction: Alcohol, tobacco or some other chemical in the environment interacts with a drug
- Drug-food interaction: For example, grapefruit causes the inhibition of several drugs
- Drug-drug interaction: A drug alters the effect of another drug.

SITUATIONS FAVORING DRUG INTERACTIONS TO OCCUR

Increased number of concurrent drugs

Cases like, where a person suffers from both congestive heart failure and hypertension, the administration of digitalis and an antihypertensive together would lead to abnormal heart rhythms, or the use of drugs which are not prescribed like aspirin or herbal preparations concurrently would lead to interactions. When a patient receives about five drugs at a time, the possibility of interaction is about 50% and this becomes 100% when seven to eight drugs are administered.

Various physicians

It is common among the people that they get their treatment for a particular disease from at least two specialists, including their family physician. It is not always essential that a physician should remember all the drugs which are prescribed for a patient by other physicians an example is that one may prescribe an antihistamine with sedative effect and another may permit the use of anxiolytic which may cause a depressive effect.

VARIOUS WAYS BY WHICH PHARMACOLOGICALLY ACTIVITY OF A DRUG CAN BE STUDIED

Most of the drugs in the market nowadays have intense capacity to act on many physiological systems. Hence, they exhibit more than one pharmacological action. Thus, two drugs administered concurrently would always have some effect on each other. The sedative effect of tranquilizers is enhanced by antihistamines.

INCREASED NUMBER OF DISEASES

People all over the world, especially in India, are prone and are deeply affected by diabetes and hypertension which are very common among people above 40. In such cases, drug interactions can be caused if multiple therapies are done. For example, there is an elevation in blood sugar level due to the decrease in response of anti-diabetic drug caused due to the oral administration of beta-blockers and hypoglycemics.

OVERDOSING OR UNDER DOSING

This is mainly due to the delay of administering drugs either due to inadequate instructions from the physician or pharmacists, or not following their instructions. Sometimes even due to the increased number of medicines, a confusion could arise leading to drug interaction.

INTERACTIONS AMONG POTENT DRUGS

Interactions among drugs like anti-hypertensives, hypoglycemics, digoxin, etc. are most likely to occur, leading to a narrow therapeutic index. Interactions in elderly patients due to low activity of liver function are also common.

PHARMACEUTICAL INTERACTION

A physicochemical interaction which occurs when the mixation of drugs in the intravenous occurs, leading to the inactivation of the active medicaments. For example, dextran interacts with chlorpromazine, ampicillin, and barbiturates forming chemical complexes.

PHARMACOKINETIC INTERACTION

This interaction is called as ADME interaction due to the alteration of absorption, metabolism, distribution, or excretion of one drug by the other. They can be classified as:

Absorption interaction

Here, the absorption of the drug is either fast or slow with complete or incomplete drug absorption.

Different ways of absorption interaction are:

- A change in gastric intestinal pH
- Syndrome causing less absorption
- Gastric intestinal enzymes being inhibited.

Distribution interaction

There is an alteration of the distribution pattern of the drug. One major way is a change in protein-drug binding.

Metabolism interaction
Change in the metabolism of the drug. It takes place by two-ways
- Enzyme is greatly synthesized for increased metabolism speed
- There is less secretion of enzyme and hence decreased rate resulting to be the most fatal among all.

Excretion interaction
The way the drug is excreted is being altered, the various methods are
- Drugs like antacids and amphetamine alters the pH of the urine
- There is competition in getting secreted actively by drugs such as penicillin and probenecid
- NSAIDs cause a reduction in the renal blood flow with lithium.

PHARMACODYNAMIC INTERACTION

The activity of one drug is altered by the other at the place of action which may either be direct or indirect.

DIRECT PHARMACODYNAMIC INTERACTION

There is a concurrent usage of drugs having either same or different pharmacological effects. The three effects of direct interactions are (1) Antagonistic effect, (2) additive effect, (3) synergistic effect.

Antagonistic effect
Noradrenaline and acetylcholine having different effects on heart rate.

Additive effect
Central nervous system (CNS), depressing drugs like hypnotics and sedatives, have the same goal, and hence there is summing up of their activity.

Synergistic effect
One drug has been given more power by the other. For example, the potential of aspirin is increased by alcohol where its analgesic activity is increased.

INDIRECT PHARMACODYNAMIC INTERACTION

Here both the drugs do not have any relating effects, but somehow there is an alteration of one drug by the other in an indirect manner. For example, aggregation of platelets leading to the impairing of hemostasis is being decreased by salicylates, if there is an induction of bleeding by warfarin [2,3].

FATE OF DRUGS WHEN INTERACTION OCCURS

Effect on absorption of drugs
It is natural that there would be an alteration in the quantity of drug absorbed or the speed at which the drug is being absorbed in the body, sometimes both when a drug is administered orally. This effect is of importance in chronic therapy and significant in acute conditions, where the administration of drugs is made through single units.

Such alterations are very rare in the parenteral drugs. It can take place when drugs like methacholine and adrenaline are taken extravascularly immediately with other drugs. Hence, there is an alteration of the absorption of the latter drugs due to constriction or dilation of the blood vessels.

There is the formation of complexes which are not easily absorbed and are insoluble with heavy metal ions like Al, Mg, Fe, Zn, Ca, Bi ions which are contained in food, mineral supplements and antacids where these are the offending drugs and the victims are fluoroquinolones, tetracyclines, etc.

There is bacterial flora destruction which causes an inactivation of digoxin in the lower part of the intestine and increases the bioavailability. Here, digoxin is the affected drug and antibiotics like erythromycin, tetracycline, etc. are the perpetrators.

EFFECT ON DISTRIBUTION OF DRUGS

There is always competition among drugs in binding to a protein molecule or a tissue and in displacing of one drug from the other. Significantly when both the drugs are eligible of binding in the same site, there is competition among drugs of displacing one from the other. In some cases, there may even be an extreme increase in the free form of the drug, which may result in increased amount of toxication and high therapeutic effects.

There is a high probability of hemorrhages and more time for clotting where the displaced drug is warfarin and displaces are chloral hydrates, phenylbutazones, salicylates, etc. In cases, drugs are displaced from tissues of their binding sites where an example posed toward this is the oral hypoglycemias such as sulfonyl; ureas such as tolbutamide and glibenclamide which expose their therapeutic effects by resulting in elevated levels. There is the displacement of insulin from the binding sites of proteins in the pancreas and other regions.

EFFECT ON METABOLISM OF DRUGS

When there is either an inhibition or induction of one drug metabolism by the other, a serious problem occurs. The major cause of the pharmacokinetic interaction being the change in the speed of biotransformation of drugs when there is a concurrent intake of drugs which undergo first pass metabolism. Enzyme inducers may even increase the toxicity of the drugs having active metabolites. They even show a reduction in the blood level. In spite of being not that harmful, enzyme inhibition may lead to toxic effects by accumulation of drugs and even serious effects could occur.

There is an increased absorption of the drugs which undergo their metabolism exclusively through the first pass hepatic system such as propranolol, calcium channel blockers, etc., by the precipitant drug, the grapefruit juice and there is a great chance for toxicity. Efficacy of drugs such as corticosteroids, coumarins, phenytoin, oral contraceptives, tolbutamide, tricyclic antidepressants, etc., is decreased by barbiturates and decreased plasma level is noted [2,3].

EFFECT ON EXCRETION OF DRUGS

Pharmacodynamic effect of drugs causes pharmacokinetic interactions between lithium and thiazide diuretics. There is retention of lithium in the body due to the influence of thiazide diuretics on the transport of sodium renally leading to toxicity. The agents which alter the biliary transport or alteration of the bile flow rate cause an interaction in excretion when it is done by biliary excretion and another major mechanism.

When a large quantity of a drug or its active metabolites is eliminated in the urine, renal interactions are said to occur. There is a decrease in the renal clearance of lithium bicarbonate by the precipitant drugs such as NSAIDs (prostaglandins control renal blood flow by vasoconstriction partially). There is an increased risk of toxicity and passive reabsorption of drugs amphetamine, tetracycline, and quinidine, due to drugs like antacids, acetazolamide and thiazides [2].

CATEGORIES OF DRUG INTERACTIONS (EXAMPLES)

Psychopharmacological agents
Antidepressants + coumarin - increased anticoagulant activity

Antipsychotic agents + antacids - decreased plasma level of the drug

Antipsychotic agents + monoamine oxidase (MAO) inhibitors - increased action of antipsychotic drugs

Sedatives and hypnotics + griseofulvin - decreased action of griseofulvin

Sedatives and hypnotics + MAO inhibitors - CNS depression

HYPOGLYCEMIC AGENTS

Insulin, tolbutamide with:

- Prednisolone: Increase in glucose level
- Alcohol: Faster hypoglycemia
- Propranalol: Increased action of insulin
- Coumarin: Increased action of coumarin
- Phenylbutazone: Increased action of insulin.

GASTROINTESTINAL AGENTS

Antacids + bisacodyl - disintegration of the enteric coating in the stomach

Antacids + tetracycline - Poor absorption due to the formation of complexes with metal ions like Ca, Mg, etc.

Vitamins

Folic acid + phenytoin - folic acid deficiency and decreased phenytoin level

Vitamin K + coumarin - antagonism

Vitamin C + aspirin - reduced vitamin C absorption

Vitamin D + phenytoin - vitamin D deficiency

Vitamin B6 + levodopa - patients undergoing levodopa therapy should avoid multivitamins.

Analgesics

Aspirin + alcohol, aspirin + ibuprofen - irritation of bleeding of the tract

Narcotic analgesics + barbiturates (CNS depressants) - depressing action

Paracetamol + metoclopramide – onset of paracetamol action.

Cardiovascular agents

Digitalis + barbiturates - increased metabolism of digitalis

Digitalis + diuretics - depletion of potassium

Digitalis + reserpine - risk of cardiac effect

Methyldopa + levodopa - additive effect

Propranolol + insulin, tolbutamide - increased action of hypoglycemia [1-3].

DISEASES DUE TO DRUG INTERACTIONS

It is really a shock that the drugs which are prescribed by the physicians to cure our diseases turn against us and produces new diseases by interacting among them. Such interactions which are caused by the drugs prescribed by the physicians and diseases produced due to this is called as Iatrogenic. The main damage due to these diseases occurs to the liver and kidney, even though damages occur to the other parts of the body such as gastrointestinal tract, skin, and blood. All this occurs only in the case of abusing or misusing the drugs. Hence, proper care must be taken in order to be safe.

Liver diseases

The damage of the liver may occur directly or indirectly by drugs. The direct damage may be caused due to the hypersensitivity of the patient toward drugs such as erythromycin etiolate and sulfonamides. These damages may be acute or chronic. Acute hepatotoxicity is due to drugs such as rifampicin, cimetidine, phenylbutazone, and erythromycin. Chronic liver diseases may be due to sulfonamides, penicillin, oral contraceptives, anabolic steroids, etc.

Renal diseases

Kidney, being one of the most important regions for the elimination of toxic substances from the body is very much vulnerable to get damaged on ageing. In the elimination of toxic substances, the kidney breaks down the protein - toxin complexes resulting in the increased concentration of toxins in the kidney. There may even be the hypersensitivity action of the complexes present in the endothelial area of the kidney. Hence, the drugs like sulfonamides which may cause kidney stone and allopurinol which may lead to uric acid crystallization should be administered with caution.

Hematological disorders

Due to induction there is the development of disorders in the blood agents like anemia and leukopenia caused by chloramphenicol, INH, phenytoin, antimalarials, analgesics, phenylbutazone, sulfa drugs, etc. Thrombocytopenia may be caused due to aspirin, ibuprofen, penicillin, alcohol, etc. These are only temporary and hence not called as diseases and they are curable.

Gastrointestinal disorders

This type of disorders depends on diet and even occurs due to antibiotics, salicylates, ephedrine, vomiting, ulceration, etc.

Dermatological reactions

It is due to the hypersensitivity reaction of the patient toward sunlight. After the administration of the drug, sudden exposure to sunlight may cause the reddening of the skin, blisters, itching, etc., of the patient's skin. It may be due to phototoxic or photoallergic, photosensitive effects.

Teratogenic effects

Teratogenicity refers to the induction caused to the somatic cells of the developing fetus, and there is damage of one or the other organ system resulting from this induction. The agents like thalidomide, diethylstilbestrol, tetracycline, etc. are called as teratogens which causes this effect. Extreme care should be taken for pregnant women in the first trimester time during the administration of these drugs. The damage if caused to the neonate is comparable with a healthy baby at the prenatal and postnatal periods [3].

DIFFICULTIES IN FINDING OUT DRUG INTERACTIONS

There are so many difficulties in detecting drug interactions. When a patient is under observation he may develop some abnormalities which are generally not passed into deeply or the physician may take it due to problems other than drug interactions such as use of drugs other than those used regularly, immunity for tolerance, etc.

Another reason which can be quoted is that physicians do not doubt on their own treatment. Hence, such an idea of drug interaction would never enter into their mind unless the condition has become adverse. Only then will they even look into the previous reports of adverse drug reactions (ADR). There cannot be any measure done for the detection of certain drugs like tranquilizers, as their potential is undetectable. Their physician may even think about his fate if a drug interaction is reported in patient, which would be full of criticisms and legal problems.

REPORTS ON DRUG INTERACTIONS

There are both beneficial and harmful activities due to drug interactions. Some of the drug interactions would result in the additive or synergistic effect of the drugs resulting in the reduction of dosage quantity. It has been noted that if probenecid is given together with penicillin, the effect is increased thus resulting in a reduction of dose quantity.

Sometimes there may be an adverse reaction between drugs, for example, warfarin interacts with aspirin. Hence, an alternative such as paracetamol can be prescribed. In another case, if tetracyclines and antacids have to be given together, then there should be an interval between the administrations of both the drugs.

All the interactions between the drugs may not be same or may not even be true among everybody. It differs from people to people. Some interactions may be noted only in animals, and the impact in humans

may not even be known. The variation of these interactions among humans may differ due to habits such as smoking, food intake and also due to other criterias like genetic, age, renal disease, hepatic disorders, and alcohol consumption, sometimes even environmental conditions may have effects on drug action.

Drug food interactions - a common problem

Thinking food and the natural herbs found in our surroundings to be safe and natural, many people make mistakes of their administration without taking any advice from their physicians. The administration of drugs along with these herbs or certain food should be carefully monitored as they would be dangerous. The passage of these drugs and food are same, and hence they react with each other producing adverse effects.

A drug-food interaction is said to be taking place when the administered food reacts with certain additives of the drugs, leading to either decreasing the efficacy of the drugs or altering the pharmacokinetic, pharmacodynamic, or bioavailability of the drugs. Elderly people suffering from chronic disease and with the intake of three or four medications should be carefully monitored from the effect of these interactions. For such people, food habits which can be handled smooth by the drugs are to be maintained. They may be people from congestive heart failure, cholesterol (high), hypertensive, etc.

Sometimes there may even be the dependence on the nutrient content of a patient for the therapeutic activity of a drug such as in the gastrointestinal tract or increase in the absorption of the drug. Mainly vitamins, iron pills, herbal preparation taken along with pharmaceutical drugs leads to serious interactions [4].

Grape - a fruit of wonder

Grapes being one of the most common liked and consumed fruit is known to contain a large amount of beneficial ingredients producing marvelous effects. Grapefruit extract is an important dietary supplement. It is found to contain polyphenolic compounds like flavanoids and resveratrol, which are very important and present to a large extent in the seeds and skin of grapes. They differ from tea polyphenols in that they contain polymers such as procyanidins, proanthocyanidins whereas tea contains rich polyphenols which are monomers such as catechins. They contain the presence of antioxidants such as procyanidins, due to this it is considered to be of high dietary importance. It has been noted that this procyanidins contains anti-allergic, anti-inflammatory, anti-arthritic activities preventing skin ageing and heart attack. They are known to contain both antioxidant and anti-cancer activities [5].

WAYS OF PREVENTING DRUG - FOOD INTERACTIONS

The effect of drug food interactions is not the same in all the people; they vary from people to people depending on their age, size, dosage of the drug and the person's health, the type of food taken and the sort of drug. Avoiding these interactions within human body does not mean avoiding these food habits or these drugs but usage of these drugs in a proper and logical manner. For example, tetracycline and dairy products should not be taken together. Instead, a break between the Administrations of these two could be far better than avoiding these products. Knowledge about these medications and time management is very essential.

PRECAUTIONS TO BE TAKEN ON CERTAIN DRUG - FOOD INTERACTIONS

Antihypertensives

Beta blockers: Empty stomach intake increases absorption. Foods life meat may cause low pressure and dizziness.

Digitalis: Reduced absorption takes place if taken with milk or high fiber foods. Potassium loss is seen.

Antiarrhythmic drugs: There is a risk of an irregular heartbeat if caffeine is taken.

Alpha blockers: Should be taken along with food to avoid decreased or sudden lowering of blood pressure.

Diuretics: Risk of potassium deficiency.

Potassium sparing diuretics: It would lead to potassium Hyperaction, should not be taken unless prescribed by the physician.

Antiasthmatics

Pseudoephedrine: Increase in anxiety and nervous action with caffeine.

Theophylline: Increase in drug toxication due to caffeine, reduction in absorption due to high protein diet.

Antibiotics

Cephalosporin, penicillin: Absorption increased when taken in empty stomach

Erythromycin: Decreased activity with wine and fruit juice

Tetracycline: Vitamin C absorption decreased, dairy products lower the effectiveness.

Anticonvulsants

Dilantin, phenobarbital: Deficiency of folate and some vitamin B causing the danger of anemia and neuro problems.

Antidepressants

Lithium: Lithium toxicity is caused with the consumption of low salt diet and efficacy is reduced with high salt diet.

Tricyclics: Reduced absorption with foods like meat, fish, legume, and vitamin C rich foods.

Fluoxetine: Leads to weight loss due to decrease in appetite.

Cholesterol lowering drugs

Cholestyramine: There is a clearance of fat soluble vitamins and folate.

Gemfibrozil: The clearance in cholesterol is not possible if fatty foods are taken on administration of this drug; should be taken after one hour after eating [5].

THE TRADITIONAL HEALER OF THE ERA – HERBS

In this fast running society there are various developments in the field of Medicine as a whole, like the entry of gene therapy, biotechnological development, etc. But still most of the people completely trust herbs to be natural. But they have adverse effects on our body. Most of the medications like morphine, atropine, digitalis, and chemotherapeutic agents have been made out of these herbs. It has been estimated by WHO, that about three-fourth of the world population still depend on these herbal drugs, where most of them take it even without the advice or knowledge of their physicians. Experts suggest that Herbs drug interactions occur very rarely and if they do occur it is due to the pharmacologically active drug, the conventional drug [6].

HERBAL DRUG INTERACTIONS

Interactions among herbs and drugs are effective in certain cases and toxic at times. Both have therapeutic uses and harming nature. The administration of herbs along with pharmacological drugs for the decrement of glucose in blood concentration may lead to hypoglycemic conditions, which is dangerous. The chances for a drug to interact are tremendous because the production of these drugs is from some 1000 chemicals which are different. Its mechanism may be subheaded into two categories: Pharmacodynamic and Pharmacokinetic interactions.

MECHANISM OF INTERACTIONS

Water soluble carbohydrates like gums and mucilages are very difficult to be absorbed when taken in powdered or other forms. Hence, they bind to other foods for their absorption. Herbs like rhubarb, flax seeds, aloe, marshmallows, etc., undergo this property. Sometimes rhubarb and Aloe would cause a reduction in the action of warfarin, digoxin, etc. hence time management should be taken for the administration of these herbs with drugs.

Adverse drug interaction takes place if salicylates which reduce pain are taken along with meadowsweet and black willow. Hence, they should not be taken together. Another effect is between liquorice and corticosteroids, leading to toxicity. There is an increase in the metabolism of drugs like protease inhibitors and cyclosporine, digoxin and theophylline, due to the induction of hepatic microsomal enzymes by St. John's Wort in cytochrome P-450 system. There is less effect of the drug in this case.

Sometimes due to this interaction there may even be the increase in activity of the drugs like, for example, Gingko increases the activity of warfarin (anticoagulants) and benzodiazepines are elevated by valerian, where hypnotic activity is increased. Hence, such interactions should be avoided.

EFFECTS OF INTERACTIONS AMONG PATIENTS RECEIVING VARIOUS DRUGS

Anticoagulants using patients

There is an increasing risk of bleeding if garlic and ginkgo are given with warfarin and coumarin. There is an inhibition of aggregation of platelet and the fibrinogen activity in healthy people and coronary artery disease patients. It is also associated with spinal epidural hematoma spontaneously. In ginkgo, platelet activating factors are antagonized by ginkgollides. Reports suggest patients to avoid quai with warfarin. The effect of warfarin was stimulated by administrating carica papaya (green fruit of papaya) and ginger. Sometimes intracranial bleeding has been reported when Ginkgo is combined with aspirin. Warfarin having a narrow therapeutic index, people administering dietary supplements along with this should be carefully monitored. Sometimes eleuthero can inhibit aggregation of platelet.

Cardiovascular medications

St. John's wort administered to the cardiac patients, cause adverse interactions. Cholesterol levels and hypertension should be noted if a patient receives this drug. In case of digoxin, its activity is decreased with St. John's wort, where its bioavailability is decreased. Ginseng increases the action of digoxin. The risk of hypertension is increased in people administering Yohimbe. Cardiac glycosides is present in foxglove and some other herbs, which have a potentiating effect with digitaloid cardiac glycosides, elevation in digoxin level is reported when it interacts with Siberian ginseng.

Psychiatric medications

St. John's wort should not be taken by patients, if they are undergoing selective serotonin reuptake inhibitor (SSRI). This decreases the activity of the psychiatric medications which are metabolized at CYP450 enzyme system. Tricyclic antidepressants and benzodiazepine levels in serum are decreased due to St. John's wort, even though they are not effective clinically.

Anti-diabetic medications

Medicinal herbs with hypoglycemic properties which are made use of for glucose control may be Aloevera, fruit of bitter melon, seeds of fenugreek. Potentiation of hypoglycemic effects is reported when herbs like ginseng are taken with insulin or other oral hypoglycemics. But care and self-controlling should be done by the patient to avoid complications.

HIV medications

The serum levels of antiretroviral drugs are decreased when herbal preparations containing St. John's wort is administered by the patient which would cause an inhibition of CYP3A4 and p-glycoprotein systems. To a small extent, the administration of garlic, vitamin C, milk thistle, Echinacea species and gold ensal would also cause the inhibition of CYP450. Hence, patients undergoing HIV therapy should be carefully handled if they undergo herbal therapies including St. John's wort [6].

AWARENESS AND COUNSELING TO PATIENTS ABOUT HERBAL INTERACTIONS

A physician should handle a patient very carefully and in a relaxed tone to get all the information about their self-administration of any herbal drugs. There may be decrease in the absorption of the drugs which get metabolized intestinally if usage of laxative and bulk forming agents are encouraged in administration. Some of the stimulant laxative herbs are cascara sagrada (*Rhamnus purshiana*), and the herbs anthranoid contained senna. It is the phytochemical present in the herbs like P450 enzymes which cause inhibition of the conventional drugs if both are administered Concomitantly. Among the herbs, kava and green tea show greater effect of herb-drug interaction, whereas other herbs like grape seed extract, ginseng, black whosh, saw palmetto, etc. may cause only a mild interaction or one which is not clinically noted. They may not react to a great extent with CYP enzymes [6].

KAVA

This is one of the most reactive herbal drug which interacts with almost all the conventional drugs. The association of rhabdomyolysis is due to the pharmacodynamic interaction between Kava and Caffeine. There is a possibility of the potentiation and additivity of kava with anti-convulsants, where side effects like lethargy and cognitive impairments are occurred. There is an occurrence of additive effect between kavalactones and MAO inhibitors made use of in the treatment of parkinson's disease. There is an inhibition of kava with warfarin and several kavalactones. There is no record of interactions between anti-platelet drugs like dipyridamole or aspirin and anticoagulants like phenprocoumon and warfarin. Kava behaves naturally in a particular manner in both the cases of pharmacokinetic and pharmacodynamic interactions with other herbs and drugs. There are certain evidence and the acceptance is based on theoretical observations and not on experimental data. Hence, the patient and the volunteers are required to gain the complete knowledge of the various interactions of the drug [7].

VARIATIONS IN HERBAL COMPOSITION CAUSING DIFFERENCES IN THEIR ACTION

The amount of active ingredient needed to produce the required effect is very essential for an interaction to occur, which depends upon the pharmacokinetic and physicochemical properties of the ingredients such as elimination, absorption, distribution, and oral bioavailability. These differences in the active compound can cause the entire action of the drug to change. These changes may even cause their biological effects to be changed from the one which has already been known and recorded. They may vary if the Manufactures may cause a change in this active ingredient of the herb. The quality of the herbal products not tackled effectively seems to be problematic to all medications. Sometimes there may be changes in the action of drug among the same batch or between different brands of the herbal products. Therefore, how much importance is given to the preparation of the prescription drugs, the same due respect and importance must be given in the manufacturing of herbal drugs [5,6].

WITHDRAWAL OF DRUGS FROM THE MARKET

The interaction of drug with food, dietary supplements, other drugs, etc., have caused adverse reactions and resulted in the removal of such drugs from supply. More than half of the drugs have faced this situation in the market. The adverse reactions of these drugs cause a lowering in the efficacy of the drug, inhibition or an induction of the drugs which causes the metabolization. Sometimes there may even be an induction

of the cytochrome P450 enzymes, thus reducing their exposure in the systemic circulation. There is complete loss of the effect of administered drugs in this case. There may be interactions due to food nutrients like vitamins in fruit and vegetables and interactions between drug and citrus fruits causing serious effects.

More of caring and considerations should be taken among the patients administering AIDS and cancer medicaments, where the intake of dietary supplements and number of medications may cause adverse interactions. The center for drug interaction and research have taken the pain to note the interaction taking place in such patients, and to make a note of it on the label of the drug as a caution, so that the providers and the administrators can avoid the risk of any interactions, if they would get affected as a small step [8].

DRUG - DRUG INTERACTIONS: AN IMPORTANT ISSUE

Many companies have come to know the need of evaluating the way the drug is eliminated from the body and the process by which they may cause changes in the enzymes or transporters present within the body under each system. Before the development of the drug, cytochrome P450 enzymes are inhibited, and the changes caused to the enzymes, like CYP1A2, CYP2C9, CYP2C19, CTP2D6, and CYP3A are detected initially before the making of the drug. The answers to these questions about how elimination and interaction of a drug takes place are performed on the tissues of liver or through expressed human enzymes. Not only the CYP enzymes in the body are affected but also other transporters like p-glycoprotein, organic anion transporting peptide, multi-drug resistance protein and other metabolic enzymes like glucuronosyl transferases also undergo drug interactions.

An example which can be posed for a clear understanding of this mechanism is as follows:

Systemic exposure of the drug is achieved only when dose ranging from 2.5 mg to 5 mg is administered every day for about 3 days. When Vardenafil is taken along with cytochrome P450 inhibitors, a safe and effective result is obtained [9].

DRUG - DIETARY SUPPLEMENT INTERACTIONS

Effect of orange, apple and grape juice on fexofenadine

Fexofenadine is a substrate of p-glycoprotein and organic anion transporting polypeptides (OATP). There is no increase in the plasma level concentration. On large administration of apple, grape and orange juice, there is a decrease in the level of fexofenadine. This is more due to the reasons that all fruit juices are potent inhibitors of OATP more than p-glycoprotein which are transporters. There is a significant increase in the levels of cyclosporine, when grapefruit is administered along with it. It may be due to the inhibition of p-glycoprotein. The consumption of cranberry juice was made by the people because it decreases the occurrence of urinary tract infection. Cranberry juice contains antioxidants like flavanoids, which is referred to as causing the inhibition of cytochrome P450, but more studies have to be done to clearly know about it [8].

DRUG INTERACTIONS IN ELDERLY PATIENTS

Drug interactions is very effective and occurs more rapidly in the elderly patients due to a number of factors, like the intake of number of medications, slowdown of the metabolizing ability of organs which eliminate toxic substances from the body, i.e., liver and kidney, in particular, and so on. In such patients as it is very easy for an interaction to occur, dosage regimens should be fixed for individual persons. If possible, it can also be extended to individual organs, as the metabolism and functioning of each organ have slowed down. Especially the drugs which cause CNS effects, the choice of drug and its dosage is of great importance. Initially, the drugs used can be of low doses and then there could be a silent increment in the dosage of the drugs so that adverse interactions in these elderly patients can be avoided.

An elderly patient is having increased level of hypercholestrol activity, less amount of elimination in toxic metabolities, low homeostasis, administering a large number of medications at a time, undergoing multiple diagnoses is considered to be a frail elderly patient. A number of drug interactions in this elderly group resulted in hospitalization. Some examples which could be quoted under this category is angiotensin receptor blockers - sulfamethoxazole, calcium channel blockers - macrolide antibiotics, lithium - loop diuretics, sulfonylureas - anti-microbial agents, angiotensin converting enzyme inhibitors, and potassium sparing diuretics.

All drugs do not produce the same action in all individuals. Similarly, among elders various drugs cause different effects among the people. Diseases which are related to the kidney would cause a large number of ADR's to occur due to the remains of toxicity within the body. The metabolism of the drug is affected during liver and cardiac diseases which affect the hepatic blood flow, if diseases which affect any other organs of the elderly patients would make them more prone to ADRs with many drugs. The discontinuation of a drug is also known to cause problems in this elderly group. There is an adverse drug withdrawal event after the discontinuation of benzodiazepines or alcohol. Hence, more knowledge about this to the patients is necessary for their safety measures. A physician should try his best to withdraw a medication out of many drugs that an elderly patient undergoes. Multiple-drug administration could cause changes in pharmacokinetic and pharmacodynamic interactions where both would cause ADR. However, it is more likely to occur in younger adults [10,11].

DRUGS INTERACTIONS WITH ALCOHOL

Drug interaction with alcohol would lead to serious outcomes. As usual, the type of interactions is pharmacokinetic and pharmacodynamic. An alteration of a drugs metabolization or its clearance would be considered to be pharmacokinetic interaction. An additive effect of the alcohol and the drug used is said to be pharmacodynamic which does not cause any changes to the pharmacokinetic properties. A number of drugs are known to interact with alcohol such as sedatives, hypnotics, antibiotics, and anti-depressants [12,13].

DRUG - NUTRIENT INTERACTIONS

A healthy diet mainly consist of fruits and vegetables which gives low energy and consist of high amounts of fibers, micronutrients and other components like phytochemicals which have functional actions. A person's diet not including fruits and vegetables would lead to a number of factors causing death with diseases like Marasmus and Kwashiorkar in children and a number of vitamin deficiencies. The World Health Organization has reported the prevention of non-communicable diseases in a healthy diet including all fruits and vegetables. Combining of some phytochemicals within this healthy administer is very effective in preventing some diseases from occurring.

The continuous uptake of such a diet would reduce the administration of foods containing saturated oils, sugars and salts which would itself lead to a number of diseases to occur. There are increased therapeutic effects when drug - phytochemical interaction or drug - dietary interactions sometimes occur. Plant products and herbal drugs have effect on the bioavailability of drugs. Some examples which can be quoted are papaya, where the phytochemicals present in it are beta cryptoxanthin and benzyl isothiocyanates, the use of it is for malaria, obesity, oral drug poisoning, discomfort in abdominal pain, diabetes and infections. Mango which is used as a laxative, diuretics, to control heart diseases which consist of phytochemicals like flavanoids, glycosylated xanthones, saponins, phenolic acids, black mulberry which contains a variety of phytochemicals like 2- aryl benzofuran derivative, mornigrol H, mornigrol D, mornigrol G, flavanol, albanin A, and E stilbenes which are used traditionally for treating inflammation of respiratory tract, in healing gastrointestinal tract etc. Orange contains flavanoids like tangeretin, nobiletin, diosmin and hesperetin, which is used for arthritis, gastrointestinal tract treatment, inflammations in respiratory tract and many others [14].

SMOKING - DRUG INTERACTION

Smoking has resulted in decline of physical, mental, and financial well-being of a person. It has put him down in the society resulting him to be addict toward this drug - Tobacco. Tobacco could affect the drugs which are taken. Due to pharmacokinetic interactions in smokers there is reduced absorption, distribution of the drugs which are taken in. Hence, it becomes necessary for them to take a large amount of doses, increment in the clearance from the plasma, induction of enzymes, etc. Nicotine present in tobacco is very additive in nature. It causes pharmacodynamic interactions in women (those who smoke), who use oral contraceptives and in men with cardiovascular diseases, ADR takes place. The liver enzymes like CYP1A2, CYP2A6, CYP2B6, and CYP2D6 which are involved in the metabolization of many drugs are enhanced due to the tar-like compounds and polycyclic hydrocarbons present in the tobacco. Thus, there is a decreased action of the drug due to quick elimination of it from the plasma. These smokers are generally prescribed higher doses of psychotropic medication than the others due to their quick elimination from both. If smoking is suddenly stopped or controlled, then there is a decrease in enzyme induction. Hence, a large amount of drug remains in their plasma concentration. As a result, the person suffers from many side effects when he suddenly stops smoking, even though the same dosage of drugs is taken. Hence, more care and concern should be taken in the person from not quitting smoking which may cause more drug related interactions. Even though such interactions are not clinically significant, care should be taken. The importance of such interactions and their danger must be borne in mind [13,15].

INTERACTIONS OF ANTIDEPRESSANTS

Antidepressants like nenlafaxine inhibits CYP2D6 enzyme, increasing the effects of amphetamines where the strongest inhibitors are proxetine and fluoxetine. Many amphetamine users are also reported to take antidepressants in practice. They should be carefully checked for any adverse reactions such as hypertension and toxication of serotonin. Methylene dioxymethamphetamine (MDMA) acts on the serotonin in the plasma.

There is an adverse reaction resulting in stimulation of cardiovascular and CNS. MDMA'S metabolization takes place by the CYP2D6 enzyme. There is an increase in toxicity of MDMA when the inhibition of this enzyme and other CYP enzymes are done. Death has occurred due to the ingestion of MDMAs, moclobemide, and phenelzine due to increase in serotonin levels. Some reports say that the administration of citalopram and MDMA showed symptoms which indicated serotonin syndrome which came to be normal after stopping use of citalopram. MDMA and antidepressants would cause hyponatremia. Risk of additive effects occur when they are taken under situations like the long timing of dancing where dehydration would occur, if SSRIs are used after taking MDMAs. Hypertensive results when cocaine and MAIOs are used together. The euphoric result of cocaine is decreased by fluoxetine. The reports which indicate these interactions are not very strong even though they are numerous. Even then it is warned not to use MAOIs with other drugs. When SSRIs and tricyclic antidepressants are administered together or taken alternately, major reactions would take place [16,17].

DRUG INTERACTIONS DUE TO CHELATION AND ITS ABSORPTION

Chelation could be clearly defined as the insoluble complexes, which consist of a ring-like structure between metallic ions like magnesium, iron, aluminum and very rarely calcium and an organic molecule. This insoluble complex formed in the gastrointestinal tract could not penetrate through the intestinal mucosa due to the decrease in drug dissolution.

Examples of such drugs which can be quoted are quinolone antibiotics forming complexes with antacids containing magnesium and aluminum, sucralfate, ferrous sulfate and some buffers. All this cations having a valency of 2 and 3 form complex with the 4-oxo and 3-carboxyl groups of this quinolones resulting in a decreased concentrations of quinolone by 30-50%. Another example is the formation of a complex between tetracycline and iron, where the concentration of tetracycline is decreased up to 80%. Adsorption would normally take place between an anti-infective and an absorbent. This would decrease the exposure of the antibiotic activity of the drug.

Acidic drugs, such as sulfonamides, doxycycline, and penicillins, are bound strongly to a smaller number of sites while basic drugs like erythromycin are weakly bound to a larger number of sites. Based on this plasma concentration and due to protein binding activities, there would be displacement of one drug by the other producing clinically significant results, which occurs with drugs which are 80-90% bound to the plasma proteins. There are large changes in free drug concentration while those which are poorly bound to plasma proteins too get displaced, but the increment in the concentration of the free drug is less. When such an interaction between protein displacements takes place, then the free drug which is increased in concentration is equally distributed entirely in the body and gets stored in the tissues if the volume is large [18].

WAYS TO AVOID DRUG - DRUG INTERACTIONS AND OTHERS

A complete knowledge on a person's drug history including administration of herbal and dietary products should be clearly known. It is easier to judge the pharmacodynamic drug interactions than the pharmacokinetic interactions. It is difficult to identify them by the clinical effects. There should be good knowledge on the pharmacological effects of drugs and about the person's condition, where the identification of additive effects of pharmacodynamic drug interactions can be identified.

Narrow therapeutic drugs would lead to pharmacokinetic drug interactions. Most of the drugs are not the perpetrators of pharmacokinetic interactions. A continuous watch for any change, decrease in efficacy of a drug, should be done like:

- An individual handbook of resources such as Australian medicines handbook helps in understanding the basic knowledge on drugs and their adverse reactions
- They contain tables which are important perpetrators of pharmacokinetic drug-drug interactions which are also available through the resources
- Drug information services have their own control on reference information which are Stockley's drug interactions and micromedex
- Keep always informing to the physician about all the medications that you administer, like dietary supplements, food diet, non-prescribed drugs etc.
- Understand and show patience to read a label completely
- After certain duration, don't forget to ask your physician to make sure that the same drugs and medications can be carried out
- When there is a sudden side effect, know how to tackle it. Identify it and inform it to the respective person
- There should not be consumption of vitamin pills along with others, unless advised to do so
- Taking medicines with alcohol or hot water is not encouraged. It should be taken only along with a glass full of water
- Do not stop taking any medications at your own wish. Always do so, if needed only at your doctor's advice
- Do not administer drugs by mixing them in water and food
- Always pose questions on your understanding which is very essential. Never feel bad or be afraid of it [9,19,20].

DRUG INTERACTION WITH PROBENECID

Other drugs	Competitive drug	Reaction
Penicillin	Probenecid	Increased penicillin action
Salicylates	Probenecid	Salicylate toxicity
Indomethacin	Probenecid	Indomethacin toxicity

CONCLUSION

There are various drug interactions with a number of factors around us. A number of steps have been taken for avoiding this interaction and special risk factors have been designed on the labeling of the affected drugs. A clear knowledge of the elimination of the new molecular entities, modulations of the CYP enzymes and some transporters is very important in understanding the interactions caused and their mechanisms. Once all this is clearly detected, there is a maximum effect to maintain safety and increase the exposure of the drug in the systemic circulation.

Unless there is clear knowledge about the pathway of drug elimination, drug interaction stands to be very difficult to be avoided. Adjustments of dosing regimens can be done only on clear understanding about the main interacting compounds present in it. Therefore, labeling of the drugs plays a major role in avoiding this risk. Drug-diet and drug-juice interactions can be avoided only when their administration is avoided.

There are a number of publications made to the public to understand these reactions. Additional risk factors of the patients have also been requested in the recently issued documents on the management of risk. To conclude, with the rapid increment in the knowledge on drug interactions and a large amount of care and concern taken, this vary from person to person depending on their body factors, etc. Hence, all steps have been taken for their easy prediction, management, not allowing their frequent recurrence, etc.

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