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Review Article

CONCEPT OF DRUG INTERACTION

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ABSTRACT
Drug interaction is an increasingly important cause of adverse reactions (ADR), and is the modification of the effect of one drug (object) by the prior or concomitant administration of another drug (precipitant drug). Drug interaction may either enhance or diminish the intended effect of one or both drugs. For example severe haemorrhage may occur if warfarin and salicylates (asprin) are combined. Precipitant drugs modify the object drug's absorption, distribution, metabolism, excretion or actual clinical effect. Nonsteroidal anti-inflammatory drugs, antibiotics and, in particular, rifampin are common precipitant drugs prescribed in primary care practice. Drugs with a narrow therapeutic range or low therapeutic index are more likely to be the objects for serious drug interactions. Object drugs in common use include warfarin, fluoroquinolones, antiepileptic drugs, oral contraceptives, cisapride and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Many other drugs, act as precipitants or objects, and a number of drugs act as both. The aim of present review is to throw light on the concept of drug interaction.

Key words: Drug, Administration, Pharmacokinetics, Pharmacodynamics, Synergism, Antagonism.

INTRODUCTION

Drug interaction refers to modification of response to one drug by another when they are administered simultaneously or in quick succession. The modification is mostly quantative, i.e. the response is either increased or decreased in intensity, but sometimes it is qualitative, i.e. an abnormal or a different type of response is produced. The possibility of drug interaction arises whenever a patient concurrently receives more than one drug, and the chances increase with the number of drugs taken[1]. Today, with the increasing availability of complex therapeutic agents and widespread polypharmacy, the potential for drug interaction is enormous. In other words phenomenon of drug interaction is defined as when the effects of one drug is changed by the presence of another drug, food, drink or an environment chemical agents. The net effect of the combination may be-

- Synergism or additive effect of one or more drugs
- Antagonism or substractive effect of one or more drugs
- Alteration of effect of one or more drugs or the production of idiosyncratic effects.

It is important to know the difference between a drug interaction and a side effect. A side effect, also known as an adverse effect, is caused by a single drug. Side effects can occur with the normal use of a drug and sometimes can be predicted and treated. A side effect, if severe enough, may require doctor to stop the drug or lower the dosage. An example of a side effect is the drowsiness caused by certain antihistamines. A drug interaction is caused by two or more drugs, foods, or other substances taken by the same person. A drug interaction may require your doctor to stop one or more of the drugs.

Types of drugs most likely to be involved in clinically important drug interactions

- Drugs with narrow safety margin, e.g. aminoglycoside antibiotics, digoxin, lithium.
- Drugs affecting closely regulated body functions, e.g. antihypertensives, antidiabetics, anticoagulants.
- Highly plasma protein bound drugs like NSAIDS, oral anticoagulants, sulfonylurease.
- Drugs metabolized by saturation kinetics, e.g. phenytoin, theophylline.

Selected examples of clinically important drug interactions

S.No	Precipitant drug*	Object drug*	Likely interaction and comments
1	NSAIDS	Ciprofloxacin and other Fluoroquinolones	Enhanced CNS toxicity, seizures; Avoid concurrent use.
2	Chronic alcoholism	Paracetamol	Hepatotoxic dose of paracetamol is reduced;doses ≤ 3 g/ day are safe.
3	Lidocane	B-blockers Quinidine and other antiarrhythmic drugs	Enhanced bradycardia and hypotension; Avoid concurrent use. Exaggerated cardiac depression, precipitation of arrhythmias; Avoid concurrent use.
4	Aspirin	Spironolactone	Reduce K^+ conserving action due to decreased tubular secretion of canrenone (active metabolite of spironolactone); Avoid concurrent use.

***Precipitant drug** is the, which alters the action/ pharmacokinetics of the other drug

***Object drug** is the drug whose action/ pharmacokinetics is altered

Examples of some nonprescription drugs that may have important interactions

People start using non-prescription drugs whenever they feel themselves to be uncomfort, and these drugs are not only available in pharmacies but also in grocery stores and convenience stores. So it's better and safe that before using such non-prescription drugs people must be aware of its interactions.

Drug	Examples
Antacids (drugs that treat indigestion, heartburn, sour stomach)	Maalox®, Tagamet®
Antiemetics (drugs that treat nausea, vomiting)	Dramamine®, Bonine®
Antihistamines (drugs that treat allergy or cold)	Benadryl®, Tavist®
Bronchodilators (drugs that treat asthma)	Primatene®, Ephedrine
Cough/**C**old/**N**asal **D**econgestant	Sudafed®, NyQuil®
Analgesics (drugs that treat body aches, pains, headaches)	Aspirin, Motrin®
Laxatives (drugs that treat constipation)	Dulcolax®, Senokot®

CAUSES OF DRUG INTERACTION[2]

❖ **Drug explosion, administration of two or more drugs simultaneously**

It is a common practice to prescribe more drugs at a time, which is reffered as "therapeutic jungle" or "polypharmacy"

❖ **Patients may refer many doctors**

Sometimes a patient is not satisfied by one doctor and may consult other doctor without informing about the consultation of the first doctor.

❖ **Irrational polypharmacy, concurrent use of prescribed and non-prescribed drugs**

A patient may take drugs like Aspirin, antacid which are available without physician's prescription. If such patients are on other drugs prescribed by physician for example digoxin or tetracycline, the drug interaction may occur.

❖ **Patient's non compliance**

Sometimes patient does not comply with the instructions given by the physician and may take food material which is being prohibited. For example cheese with monoamine oxidase inhibitors, this may result to severe hypertension crisis.

TYPES OF DRUG INTERACTION

Depending on the type of the effect produced, drug interaction may be classified as inhibiting drug interaction, potentiating drug interaction or modifying drug interaction.

Inhibiting drug interaction: An inhibiting interaction partially or completely prevent a drug from exerting its action thus diminishing its effect in the patient. Antagonism, a type of inhibiting interaction occurs when a drug with a given activity is blocked by a drug with a nullifying action e.g.

- Amphetamine and barbiturates
- Morphine and naloxone
- Adrenaline and propanolol

Potentiating drug interaction: A Potentiating interaction enhances the toxic or therapeutic effects of a drug in patients. Synergism, supra-addition, modification, absorption, distribution, metabolism and excretion of drug or modification of the drug action at receptor or sites may be involved.

Synargism, a type of potentiation, occurs when the combined effect of two or more drugs, acting simultanesouly is greater than the sum of the individual effects produced when each drug is administered alone e.g.

- Levodopa and carbidopa
- Sulfonamide and trimethoprim
- Isoniazid and rifampicin

Modifying drug interaction

FACTORS RESPONSIBLE FOR DRUG INTERACTION

Following are some factors which are responsible for drug interaction

- **Insufficient knowledge:** Inadequate understanding of the pharmacokinetics and pharmacodynamics of the drug may lead to drug interaction.
- **Dietary factors:** Constituents of an individual's diet including food stuff-vegetables which may interact with certain drugs.
- **Physiology of the individual:** Factors such as age, sex, weight and genetic abnormalities influence the occurrence of drug interaction.
- **Presence of disease states:** Pathological conditions like liver disease, kidney damage or altered enzyme systems may affect the handling of drugs by the body and lead to adverse drug interaction.

REGULAR MEDICATION DRUGS LIKELY TO BE INVOLVED IN DRUG INTERACTION

1. Antidabetics
2. Antihypertensives
3. Antianginal drugs
4. Antiarthritic drugs
5. Antiepileptic drugs
6. Antiparkinsonian drugs
7. Oral contracepatives
8. Anticoagulants
9. Antiasthmatic drugs
10. Psychopharmacological agents
11. Antipeptic ulcer drugs
12. Corticosteroids
13. Antitubercular drugs
14. Anti-HIV drugs

MECHANISM OF DRUG INTERACTION[3]

Drug interactions can be broadly divided into pharmacokinetic and pharmacodynamic interactions.

Pharmacokinetic interaction: Pharmacokinetic interactions are those which can affect the process by which drugs are absorbed, distributed, metabolized or excreted.

Pharmacodynamic interaction: Pharmacodynamic interactions occur due to modification of the action of one drug at the target site by another drug, independent of a change in its concentration. This may result in an enhanced response (synergism), an attenuated response (antagonism) or an abnormal response.

Synergistic interaction – If two drugs with similar pharmacological effects are given together, the effects can be additive. Although not strictly drug interactions, the mechanism frequently contributes to adverse drug reactions. For example, the concurrent use of drugs with CNS depressant effects, such as antidepressants, hypnotics, antiepileptics and antihistaminics, may lead to excessive

drowsiness; yet such combinations are frequently encountered.

Drug	Combined drug	Effect
Aspirin	Paracetamol	Synergestic action as analgesic/ antipyretic
Nitrous oxide	Ether	Positive effect as general anaesthesia
Ephedrine	Theophylline	Synergism as bronchiodiodilator
Sulfadiazine	Sulfamethazine	High antibacterial activity
Glipizide	Metformine	Beneficial hypoglycaemia occur
Benzodiazepines	Propranolol	Additive action and propranolol decreases sympathetic activity
Minoxidil	Nifedipine	Additively cause arteriolar dilation
Losartan	Captopril	Both act as synergism to cause hypotension
Isoniazid	Pyridoxine	One of the therapeutically applied combinations.

Antagonistic interaction – It is to be expected that a drug with an antagonist action at a particular receptor type will interact with antagonists at that receptor.

Drug	Combined drug	Effect
Atropine	Acetycholine	Both the drug diminished each other's effect
Epinephrine	Propranol	Competitive antagonism occur
Dopamine	Acetycholine	Antagonism to each other in case of parkinsonism
Androgen	Danazol	Danazol compelolunely inhibit androgen
Megestrol	Mifepristone	Mifepristone antagonised Megestrol efficacy
Flumazenil	Alprazolam	Flumazenil antagonised Alprazolam activity comparatively
ADH	Furosemide	Competitive antagonism happens

CENTERS FOR GETTING INFORMATION ABOUT DRUG INTERACTION[4]

Following are good places to get information about drugs, including drug interactions:

Pharmacist: Most accessible. Also, pharmacists have the greatest knowledge about interactions.

Doctor: A good source, but often not available and not as knowledgeable about interactions.

For prescription drugs: Look at the label and any accompanying information, such as brochures or fact sheets given with the prescription.

For over-the-counter drugs: Look at "warnings" or "drug interaction precaution" section on label. It often will say which drugs or foods may interact with the product or which drugs or foods to avoid.

Patient-oriented sources: Listed below are some examples of drug information books written for the public.

- The Complete Drug Reference, published by Consumer Reports.
- The USP Guide to Medicines, published by Avon Books.
- What Do I Take? A Consumer Guide to Nonprescription Drugs, published by the American Pharmaceutical Association.

IMPORTANT TIPS FOR AVOIDING DRUG INTERACTION

- ✓ With each visit to the doctor, inform him or her of all the medications (including prescription drugs, OTC drugs, home remedies, and herbal medicines) that you are taking.
- ✓ Get all prescriptions filled at the same pharmacy.
- ✓ Read the drug labels very carefully.
- ✓ Read directions, warnings, and interaction precautions printed on all medication labels.
- ✓ Take only drugs prescribed for you.
- ✓ Have your medications thoroughly reviewed by your doctor or pharmacist once a year.
- ✓ Know what to do if you have new symptoms or side effects. Know whom to contact and how to reach them.
- ✓ Take medicine with a full glass of water.
- ✓ Don't stir medicine into your food or take capsules apart unless directed to do so.
- ✓ Don't take vitamin pills at the same time you take medication without checking first with your doctor or pharmacist.
- ✓ Don't mix medicine into hot drinks.
- ✓ Never take medicine with alcoholic drinks.
- ✓ Don't stop taking a drug without checking with your doctor.
- ✓ Don't keep old or expired medicines in your medicine cabinet.
- ✓ **Don't be afraid to ask questions**. This is the most important tip of all and cannot be stressed enough!

CONCLUSION

Present review concludes that people should posses sound knowledge of drug interaction before using a particular drug or two or more drugs at a same time, in order to have safe medication. There are many drugs which commonly involve in interaction process and their harmful effects are also discussed.

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