Review Article

Drug Interactions: A Succinct Review

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ABSTRACT

Drug interactions are an imperative source of drug related problems which include significant morbidity and mortality. A drug interaction can be referred to as a situation in which a drug affects the activity of another drug when administered together. The drug interaction mechanisms can be pharmacokinetic, pharmacodynamic and pharmaceutical. A clinical pharmacist plays a vital role in the management of potential drug interactions. This review highlights about the mechanisms of various drug interactions alongwith role of pharmacist in order to manage them.

Keywords: Drug interactions, Pharmacokinetic, Pharmacodynamic, Pharmacist.

INTRODUCTION

Drug-induced morbidity has been considered as a universal problem which significantly contributes to large economic burdens for the society.[1-2] In diseased circumstances, the patient taking drugs in combination results in the alteration of the pharmacological activity, a phenomenon termed as drug interactions.[3-4] The risk of drug interactions with concomitant use of multiple medications is a clinically relevant issue. A drug interaction is considered clinically significant when it has been known to occur between two or more co-administered agents, resulting in the need for dosage adjustment of one of the agents. However, the mechanism of drug interaction depends upon pharmacokinetic, pharmacodynamic, and pharmaceutical interactions.[5-7] Moreover, the drug interactions can be divided into three types, i.e., drug-drug interaction, drug-food interaction, and drug-conditioned interaction.[8-10] Drug-drug interactions have been known to occur when two or more drugs react with each other; whereas, drug-food interactions result from drugs reacting with foods; and drug-condition interactions occur when an existing medical condition makes certain drugs potentially harmful.[8-10] The alteration in absorption, distribution, metabolism and excretion has been noted to result due to drug interactions.[11] In addition, various risk factors have been reported to occur due to drug interactions which include high risk patients and use of high risk drugs.[12-13] However, clinical pharmacist plays a vital role in the management of various drug interactions.[14-15] This review article discusses about various alterations and risk factors associated with drug interactions. Moreover, the role of clinical pharmacist to reduce and manage the potential drug inteartions has been delineated.

Drug interaction mechanisms

The potential drug interactions can be attributed to pharmacokinetic, pharmacodynamic, and pharmaceutical interactions.[3-4] In addition, some drug interactions have also been reported due to the combination of mechanisms. The pharmacokinetic interactions occur when one drug affects the absorption, distribution, metabolism or excretion of another drug. Moreover, a change in blood concentration causes a change in the effect caused by the drug. The pharmacodynamic interactions are due to the competition at receptor sites or activity of the interacting drugs on the same physiological system. However, no change in the plasma concentrations of interacting drugs is seen. Further, the pharmaceutical interactions can be classified as those interactions that occur prior to systemic

administration.[5-7] However, such interactions can be physical or chemical with no visible indication of a problem.

The drug absorption can be changed by many ways like gastrointestinal motility, gastrointestinal ph, solubility of drug, and protein carrier activity. In the mechanism of adsorption, the drug completely adsorbs on the surface of binding agents, and hence no drug is available in blood for action. This contention is supported by the fact that a decrease in tetracyclines serum levels occured when given with the polyvalent metacations like iron and aluminium.[16] Addiontionally, drugs like prokinetic agents has been noted to enhance the peristaltic movement of intestine wall, ultimately altering the drug absorption of intestinal wall resulting in decreased concentration of drug into the blood. Moreover, alterations in the gastrointestinal pH affected the drug absorption, as most drugs are present in ionised or non ionised form. The nonionised drugs have been noted to be easily absorbed as compared to ionised drugs. However, some drugs require acid medium for absorption and other need basic medium hence any alteration in the gastric pH affect the drug absorption, which is evidenced by the fact that antacid given with zalcitabine results in decreased absorption.[17] Moreover, the absorption of some drugs may be altered if they are taken with food and other mineral contents, especially in fat containing materials, the reason being attributed to formation of drug complexes, for eg., formation of complexes when tetracycline is given with milk.

The drug interactions may also occur due to alteration in the drug distribution within the body. The dislodgment of one drug by another from the binding sites on plasma proteins has been previously put forward as the mechanism for many drug interactions.[18] However, the mechanism involved in this type of interaction may be attributed to the competition between the drugs binding to the plasma protein with same affinity.[18-19] Thus, the drugs reaching firstly to plasma protein binding site replaces the other drug from its binding sites, ultimately leading to decreased therapeutic action of that drug, eg., non steroidal anti-inflammatory drugs when given with methotrexate resulted in the inhibition of effect of methotrexate.[20]

Furthermore, various drug interactions have been noted to occur due to alteration in metabolism. Most drugs undergo metabolism to more water-soluble compounds, before excretion in the urine. However, the drug interactions affecting metabolism are often clinically significant and can involve induction or inhibition of enzymes. As it has been well reported that the enzyme involved in drug metabolism are activated by nuclear receptors like cytochromes P_{450}.[21] Hence, it can be stated that metabolism-induced interaction may occur due to enzymatic stimulation, that may be enzymatic induction or inhibition which is supported by the fact that when two drugs are given in combination, and it either of the drug has been found to be metabolized by cytochrome P_{450} results in decrease of therapeutic effectiveness of another drug and vice-versa.[3,18,21]

In addition, it has been noted that the free fraction of drug or metabolite of drug present in blood plasma have been excreted by the kidney. However, the drugs which are strongly bound with plasma protein are not excreted by kidney. The mechanisms involved in urine excretion involve glomerular filtration, tubular secretion, and tubular reabsorption.[22] It has been found that when drugs are taken in combination, they compete for the same binding site with same affinity resulting in alteration of one drug by secretion of another drug, which is evidenced by fact that when probenecid is given with penicillin, probenecid alters the active tubular secretion of penicillin resulting in increased plasma levels of penicillin in order to enhance the therapeutic effect of penicillin.[3] Moreover, it has been widely accepted that drug are considered as weak acid and weak bases, where, the weakly acidic drugs are reabsorbed in acidic urine, while the basic drugs reabsorbed with basic urine, eg. thiazide causes the enhanced reabsorption of lithium leading to lithium toxicity.[23-24] In addition, the urinary excretion and pH play a significant role in drug interaction, which evident from the

fact that, various drugs are found to alter the excretion rate and amounts of drug by competitive inhibition of reabsorption.[25]

Risk of drug-drug interactions

It has constantly been a topic of concern that many patients suffer from greater risk of drug interactions. However, there have been a number of patient categories that are at greater risk of experiencing a drug interaction.[12] Also, there are some drugs which are liable to be involved in the more important clinically significant drug interactions (Table 1). However, certain risk factors have been found to be associated with drug interactions which include high risk patients; and high risk drugs.[12-13] It has been widely accepted that older patients are more sensitive towards the drug interaction of more drugs, eg, patients taking more than six drugs in combination enhanced the chances of drug interaction by 80%.[26-27] Further, drugs with lower therapeutics index have also been noted to cause potential drug toxicity. Hence, the pharmacokinetic interactions which alter the plasma concentration lead to change in therapeutic effect of drugs, eg., drugs that alter the pharmacokinetics like warfarin, causes the alteration in therapeutic action.[28] Other classes of drugs with important interactions include antidepressants, antiarrhythmics, antipsychotics, and hypoglycemic agents.[29-30]

Role of clinical pharmacist in drug-drug interactions

Pharmacist play a significant role in the improvement and management of drug interaction in patients presented with them. In addition, the ability to recognise and manage drug interactions has been regarded as a crucial role of the pharmacist in optmising the patient outcomes.[14-15] An important skill involves the skill to recognise clinically significant drug interactions and provide management advice to the patient and the physician, which include discussion of dose alteration strategies or alternative non-interacting drug combinations[31-32].

Clinically, the drug interactions are considered significant when it occurs between two or more agents administered together, and results in the need for a dosage adjustment of one of the agents or other medical intervention.[33-34] The withdrawal of medications such as terfenadine, astemizole, cisapride, and mibefradil from the market due to lethal drug interactions evident the significance of drug interactions. Many drug interactions can be reduced and managed if sufficient time and precaution is taken by the patient and the pharmacists. However, the work of pharmacists is to provide patient counselling and the safe use of prescription and non-prescription medication.[35] Moreover, drug interactions can be managed when a pharmacists takes adequate patient data including-age, sex, drug allergies, and history of disease. In addition, information about patient's disease and drug monitoring measures must be provided, which may be beneficial for the pharmacist in order to monitor the patient's disease and other therapeutic parameters.[12] By collecting the patient's therapeutic disease data, the adjustment can be made in drug regimen which might help in the management of drug interactions. Moreover, if two drugs given in combination, are supposed to produce the interaction and cause harmful action, the pharmacists should consult the patient and physician in order to change the medication in order to prevent further interaction caused by them.[36-37]

CONCLUSION

Worldwide, people depend on medications in order to prevent, cure, or reduce the expanding list of diseases. However, drug interactions have been known to occur which enhance the rate of morbidity and mortality associated with them. Hence, novel specialised research is essential in the early stages of drug development in order to identify potential drug interactions, define the mechanisms of older interactions, and examine the safety of new drugs that are known to cause interactions.

Table 1: Common Drug Interactions

Class of Drugs	Effects	Interaction of drug
Tetracycline	Poor absorbtion of tetracyclines	Milk
Amino glycoside	Hearing problem, kidney problem	Oral ethacarynic acid
Anti diabetic	Lower blood sugar	Non cardioselective beta blocker
Anti arrhythmic drug (Amiodarone Bretylium)	Cardiac arrhythmias	Azithromycin Clarithromycin
Warfarin	Increased risk of bleeding	Chamamile
Iron salts (Ferrous sulphate, Iron dextrin)	Fever, hypotension	ACE inhibitor (Benazepril, Captopril Analapril)
Phenytoin	CNS and Respiratory depression	Orphenadrine
Barbiturates	Muscle weakness,Reduced consciousness, coma	Phenytoin
Lithium	Hypothermia	Diazepam
Alprazalon, Diazepam	CNS depression, sedation	Clarithromycin, Erythromycin
Non depolarizing muscle relaxants (Pancuronium, Vecuronium)	Severe respiratory depression	Magnesium salt (magnesium sulphate)
Warfarin	Haemorrhage	Metronidazole
Methotrexate	Bone marrow suppression	Tetracyclins
Benzodiazepines	Sedation and Respiratory suppression	Protose inhibitor (Ampravir, Atazanavir, Darunavir)
Ethanol	Additive CNS effect, Death	Barbiturates
Predmisone	Edema	Montelukast
Theophyllines	Insomnia, seizures, restlessness	Ticlopidine
Miconazole	Severe hypoglycaemia	Oral hypoglycemic agent

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