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CLINICAL SIGNIFICANCE OF DRUG-DRUG INTERACTIONS: A REVIEW

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ABSTRACT

Drug- drug interactions (DDIs) are frequent at hospital admission, during hospital stay on a medical ward and at hospital discharge. Potential drug interactions are common in inpatients due to the complexity of pharmacotherapies administered. DDIs can lead to a variety of adverse events and adverse drug interactions. This review was undertaken to determine the prevalence of drug interactions as well as their clinical significance. Prescriptions with seven or more drugs, poly pharmacy, multiple diagnoses, and increased length of stay were determined as associated risk factors of drug- drug interactions. Improved awareness among prescribers is required to reduce the risks associated with DDIs.

Key words: Drug-drug interactions (DDIs), Inpatients, Co-morbidities, length of stay.

INTRODUCTION

Drug interactions are one of the important factors that modify response to a drug. A drug interaction said to occur when the effects of a drug is altered by another drugs, food, drink or an environmental chemical [1]. This definition applies to interactions of drugs with other drugs (drug-drug interactions), as well as drugs with food (drug-food interactions) and other substances. These are important, yet under-recognized contributors to medication errors [1]. Drug interactions can occur both in vivo and in vitro. Drug interactions outside the body can occur when different drugs are mixed in an intravenous infusion. Drug interaction inside the body can be pharmacodynamic or pharmacokinetic in nature. Pharmacodynamic interaction affect pharmacological effect of drug involved. These interactions result in synergism, antagonism, alteration of the effect or an immune mediated idiosyncrasy. Pharmacokinetic interaction affect absorption, distribution, metabolism or elimination. In pharmacokinetic interaction, the blood levels of given agents may be raised or lowered based on the type of interaction. When a therapeutic combination of a drug can lead to an unexpected change in the condition of the patient, this will be described as an interaction of potential clinical significance [2]. Drugs are one of the health technologies that are essential for the effectiveness of the care delivered at hospitals. Due to the complexity of the pharmacotherapy involved in simultaneous use of several drugs and various therapeutic classes, inpatients are at an increased risk for drug interactions. The predisposition to drug interactions is complicated by disease severity and organ failure, both of which can change the pharmacologic response to medications. Drug interaction can cause undesirable patient responses, with effects ranging from treatment inefficacy to serious adverse events [3]. Evidences from epidemiologic studies suggest that DDIs contribute to 6-30%of adverse events with significant hospitalizations or death; however the decision to prescribe two drugs simultaneously is sometimes intentional, with the aim of obtaining a specific pharmacological synergism. Potential drug – interactions can be a very important ancillary factor for the occurrence of adverse drug reactions and adverse drug events. DDIs are a subset of ADRs, accounting for about 3-5% of all ADRs and ADRs can of course be harmful or fatal [2]. An increased awareness of potential

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drug – drug interactions, rational co- prescription of drugs and a close monitoring of patients in whom these drugs are prescribed is recommended [4].

CLASSIFICATION OF POTENTIAL DRUG INTERACTIONS

All the diagnoses are coded according to International Classification of Disease (ICD-10) and drugs coded using Anatomical Therapeutic Classification (ATC) classification. All the prescriptions are checked for drug interactions using drug interaction checker soft wares.

Drug interaction checker software identifies the interactions, provides information about the associated clinical consequences or adverse reactions to drugs and characterizes the interaction mechanism. The soft ware classifies the interactions in different categories according to:

- Severity-contraindicated, severe, moderate, mild, unknown.
- Time of onset-immediate, delayed.
- Six scientific documentation categories-excellent, good, fair, poor, unlikely, unknown.
- Mechanism-pharmacokinetic, pharmacodynamic.
- Phamacokinetic interactions-based on the process involved(i.e. absorption, distribution, metabolism, elimination)
- Pharmacodynamic interaction-based on synergism and antagonism [5].

FACTORS INFLUENCING DRUG- DRUG INTERACTIONS

Drug related adverse events have been identified as a major source of morbidity and mortality in the United States, and drug – drug interactions are significant source of these events. Frequency of potential DDIs and the risk factors has widely been investigated in the hospitals. Elderly, critically ill patients are particularly vulnerable to adverse events from drug interactions because of the additional presence of multiple co-morbid disease states. The predisposing factors of drug interactions may be patient related or drug related. Drug related factors involved in drug – drug interactions include drug with narrow therapeutic indexes, drugs that prolong QTc interval, the administration of cytochrome p450 inhibitors and inducers and the drug affect glycoprotein P. The prevalence of potential DIs is associated with the number of drugs administered. The clinical significance of a DI is determined by the severity, the drug profile, and the clinical consequences for the patient and the available evidence for the interaction [6].

The administration of drugs with a narrow therapeutic index is an important predictor of DIs. The pharmacotherapy of critically ill patients requires the use of cyclosporine, tacrolimus, phenytoin, gentsmycin and vancomycin, in addition to other drugs with narrow therapeutic indexes. The identified association is likely due to the use of these drugs. The association discovered between the occurrence of DIs and the administration of drugs that prolong the QT interval should be stressed because there is a growing concern regarding these drugs due to the risk of cardiotoxicity with torsade de points and cardiac arrest. These adverse events can be determined by potential pharmacokinetic interactions that inhibit the metabolism of drugs with this property or by pharmacodynamic synergism. The metronidazole +amiodarone, fluconazole+haloperidol, fluconazole+ sulfamethoxazole+trimethoprim and amidarone+ haloperidol interactions can produce the mentioned adverse effects [7].

The administration of cytochrome P450 inhibitors and inducers and the drugs affect glycoprotein P is associated with the occurrence of DIs. The activities of cytochrome P450 and glycoprotein P are determinants of important pharmacokinetic processes in a significant number of drugs and are involved in the mechanisms responsible for DIs. The integration between basic and clinical research is essential for identifying the mechanisms and severity of those interactions. Among the mechanisms of the potential DIs, the pharmacodynamic mechanism showed a subtle predominance over the other possible mechanisms. An analysis of the pharmacokinetic interactions showed that drug metabolism is the main determinant pharmacologic process responsible for these interactions. Therapeutic failures and adverse reactions are negative outcomes associated with the identified potential interactions. Drug interactions are also relatedwith patient related factors such as age, sex, co-morbidities, length of hospital stay, polypharmacy and average number of medications prescribed. Drug interactions are common in elderly patients which suggest that there is a chance to increase drug interactions with increase in age. The association between patients with DDI and male gender is considered to be statistically significant. Patients with 2or 3 co-morbidities found to be an important risk factor of drug – drug interactions. According to ICD-10, classification the most common co-morbidities are coronary artery disease with hypertension or diabetes , hypertension with liver disease, diabetes with renal dysfunction and coronary artery disease with digestive disorder. The most commonly occurring disorder in the elderly inpatients is diseases of the circulatory system. This is followed by diseases of the digestive system in the second rank and endocrine, nutritional and metabolic diseases in the third place. Drug- drug interactions are increased in patients with the average number of medications prescribed more than 5 drugs and with increased length of stay. The prevalence also increased with the drug groups involved in the medication chart. The length of stay was significantly greater among patients who presented potential DI during hospitalization [8].

POTENTIAL DRUG INTERACTIONS IN INPATIENTS

Drugs acting on cardiovascular system alimentary tract are the most prevalent drug classes involved in drug interactions. The topmost identified interacting drugs were aspirin, or combination of aspirin and clopidogrel along with anticoagulant of high severity. The use of anticoagulant with aspirin or along with clopidogrel prolongs the clotting time resulting in an increase potential for bleeding.The second top most identified interacting drugs are combination of clopidogrel and proton pump inhibitors (except pantoprazole). Among patients receiving clopidogrel and concomitant therapy with proton pump inhibitors other than pantoprazole is associated with a loss of the beneficial effects of clopidogrel and an increased risk of re –infarction. Omeprazole has been shown to inhibit the antiplatelet activity of clopidogrel by inhibiting CYP2C19. Competitive interference within the P450 pathway can conceivably lead to a reduced amount of clopidogrel undergoing biotransformation to the active drug required to effect a change in platelet inhibition. The most frequent pharmacodynamic DDIs are heparin+streptokinase. Both increase anticoagulation and can lead to hemorrhage. The contraindicated DDIs are linezolid and dopamine/ norepinephrine. Linezolid increases effects of dopamine/norepinephrine by pharmacodnamic synergism leading to acute hypertensive episode [9].

Potential interactions leading to increased absorption of drug are detected with K^+ sparing diuretics, statins, corticosteroids and macrolide antibiotics. Potential drug interactions leading to decreased absorption of drugs are vitamin B complex, PPIs, antiepileptics, iron salts, fluoroquinlones etc. Drug displacement reactions are common between drugs having high plasma protein binding. A potential alteration in distribution of one drug by another by competing for plasma protein binding is common between drug groups like NSAIDs, beta lactam antibiotics, and antiepileptics. A possible risk of increased metabolism is detected between antitubercular drugs; AKT with antiemetic; K^+ sparing diuretics with cardiac glycosides and nitroimidazole antibiotics with antiepiletics and statins. Some drug groups are detected to have the potential to decrease the metabolism of other drugs e. g. AKT decreasing the metabolism of steroids, benzodiazepines, antiemetic, PPIs and statins. Altered excretion of one drug by another is detected as a potential DDI between several drug groups e.g. CCBs with cardiac glycosides, beta lactam antibiotics with NSAIDs with vitamins and potassium sparing diuretics with cardiac glycosides. The common mechanisms involved in these interactions are one drug affecting reabsorption or renal tubular secretion of other drug. The drugs that are predominantly secreted by renal tubules or are reabsorbed in kidney are primarily involved in these reactions e.g. beta lactam antibiotics, cardiac glycosides, NSAIDs, diuretics etc. Altered excretion of a drug can manifest as therapeutic failure or drug toxicity. A close monitoring of renal function and individualization of doses is indicated in patients who are co-prescribed these drug groups, to prevent such complications. An increased risk of rhabdomyolysis is detected due to a potential DDI between niacin and statins. Clinically significant rhabdomyolysis can be life threatening and the actual incidence is higher than reported. The risk of statin induced myopathy is increased by niacin. Ondansetron is also a frequently prescribed drug which is known to increase QTc interval and can lead to serious interactions when co-administered with other drugs which can increase QTc interval. QTc prolongation is an important adverse event with some commonly used drugs like fluroquinolones, quinidine, chloroquine, haloperidol etc.A potential increase in the risk of toxicity of one or more drug was common when antitubercular drugs are prescribed together. A possible risk of renal toxicity of aspirin is detected when co-prescribedwith drug groups like ACE inhibitors and AR blockers. This type of interaction can be particularly important in elderly patients with compromised renal function. Proton pump inhibitors are detected to increase the risk of toxicity of cardiac glycosides by producing hypomagnesaemia [10].

CONCLUSION

Potential drug interactions are frequent among inpatients prescribed multiple medications. Prevalence of drug interactions increase by a linear mode according to number of drugs prescribed, number of diagnosis, number of therapeutic drug classes, patient's gender and age. Knowledge of potential DDIs can aid in developing preventive practices and policies that allow public health services to better manage this situation. The most important factor to mitigate the patients harm is the recognition by the prescriber of a potential interaction followed by appropriate action. An increased awareness of potential DDIs, rational co-prescription of drugs and a close monitoring of patients in whom these drugs are prescribed is recommended.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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