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Original Article

Clinically Relevant Drug-Drug Interactions and Management Strategies: A Hospital-based Study

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ABSTRACT

Background: Drug-drug interactions (DDIs) are one of the significant drug-related problems encountered in clinical settings. A better understanding of the mechanisms, severity, and likely consequences of clinically significant DDIs are essential for proper medication therapy management (MTM). This study is conducted with the aim to aware clinical practitioners about clinically significant DDIs that occur in clinical settings and help them manage such events with appropriate knowledge and technique. **Methods**: A descriptive cross-sectional study was conducted at Shree Birendra Hospital, Kathmandu on the prescription of the medical out-patient department. A total of 483 prescriptions were selected randomly. A panel of physicians, pharmacologists, and clinical pharmacists under the supervision of a consultant physician was formed for verification of the reported DDIs using MICROMEDEX DRUG-REAX, Evaluation of Drug Interactions, Drug Interaction Facts, and Drug Interactions: Analysis and Management. The main outcome measure was obtained by the supervisor's endorsement of panelists' opinions about the clinical importance of DDIs.

Results: A total of 2006 medicines were prescribed in 483 prescription samples. The number of drugs per prescription was in a range from 2 to 11 with 4.15 on average. DDIs were found in 21.53% prescriptions (n=104). 168 DDIs were identified with major 32 (19%), moderate 85 (51%), and minor 51 (30%) types. As per occurrence, the panel determined that 13 interactions were clinically significant.

Conclusion: The clinically significant DDIs identified by the panel are likely to occur in clinical settings. These can be preventable and can also be used for the beneficial effects in MTM based on the critical judgment of clinical staff and patient compliance. Adequate knowledge regarding the nature of DDIs, the inclusion of automated systems, and the inter-professional collaboration of a clinical team are liable to prevent and manage such events that help in rational drug therapy.

Keywords: Medication therapy management; Outpatients; Drug interactions; Prescriptions; Medication systems

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INTRODUCTION

In the last few decades, medicine has become a leading reason for reduced mortality and disease burden.[1] However, there is ample evidence that the co-administration of multiple drugs has caused many adverse effects, which may sometimes be very serious.[2] The age-related physiological changes and associated pharmacologic profile of drugs, comorbidities, poly-pharmacy, and complex medication regimen to manage diseases make the serious drug-drug interactions (DDIs) more likely to occur.[3] Clinically relevant DDIs are those interactions, which are harmful most likely in case if we fail to identify them.

Adverse drug reaction (ADR) is one of the major causes of hospital admission of which drug interactions are more common.[4] Though the study of the potential of DDIs is an important part of drug development and market approval; comprehensive knowledge on DDIs and method of identifying potential interactions is a must for the health professionals in order to reduce the medical and economic losses.[2] Drug interaction may lead to an altered response in terms of both safety and efficacy, where concomitant administration of the drugs may alter the absorption, distribution, metabolism, or excretion of the object drug. In vitro, in silico, and simulation are some of the methods that may help in prediction of DDIs.[5] Most often drug interactions are predictable and preventable.[6]

Thus timely recognition of the potential drug interaction will prevent an undesired effect and help to achieve the goal of good clinical practice and offer an increase in drug safety.[7] It helps in proper medication therapy management (MTM) with the rational use of drugs.[8] In order to improve patient safety in the area of DDIs, identification of clinically important DDIs based upon a systematic review, and better strategies for prevention should be implemented through coordination among clinicians, pharmacologists, and pharmacists.

In this study, we aim to alert the clinical practitioners regarding clinically relevant DDIs and make strategies to manage such events.

MATERIALS AND METHODS

Study design and setting

A retrospective cross-sectional study was conducted in Shree Birendra Hospital on the prescription of medical out-patient department (MOPD) from March 2020 to August 2020. The ethical approval to conduct this study was obtained from the Institutional Review Committee of Nepalese Army Institute of Health Sciences, Kathmandu. Shree Birendra Hospital is a tertiary care level teaching hospital located in Chhauni, Kathmandu, Nepal. It is a central referral center for army personnel, veterans, and their dependents.

Participants

A panel composed of four specialists with proficiency in drug interactions consisting of consultant physician with expertise in nephrology and internal medicine (AS) as a supervisor, expert in pharmacology and clinical pharmacy (SK), hematology and internal medicine (RJ), and orthopedics (MTM) was formed. The panel was supported by the other three experts, a clinical pharmacist (SD), an internal medicine resident (SA), and pharmacology and clinical pharmacy expert (BK) for examinations, preparation, and verification of reports of DDIs.

Interventions

A total of 483 prescriptions were selected randomly. Drug interaction checker system such as MICROMEDEX DRUG-REAX, Evaluation of Drug Interactions, Drug Interaction Facts, Drug Interactions: Analysis and Management was conducted. The main outcome measure was obtained by the supervisor's endorsement of panelists' opinions about the clinical importance of DDIs.

A three-stage process was carried out for the identification of clinically relevant DDIs. The reports were then evaluated by a panel of experts using a DDI checker website. Object and precipitant drugs were identified for each interaction. Object drugs are those whose therapeutic effects get altered with the action of precipitant drugs.

Selection of Candidate DDIs

As a stage I, candidate DDIs from existing drug interaction compendia were selected. Interactions were graded as major, moderate, or minor referring to the four commonly used DDI compendia [Evaluation of Drug Interactions[9], Drug Interaction Facts[10], Drug Interactions: Analysis and Management[11], and MICROMEDEX (DRUG-REAX[12]) system] and then cross-referenced to each other. Specific criteria for the rating were developed as all compendia may differ in a rating system for DDIs. In case of being listed in three of the four compendia, DDIs were selected for further review. The interactions associated with products not

perceived from prescription such as alternative medicines, foods, or alcohol were not taken into consideration. Prescriptions from patients visiting sub-units in the MOPD such as nephrology and diabetic OPDs or visiting OPDs but including MOPD were evaluated. Prescriptions from OPDs other than medical OPD, wards, emergency, and intensive care unit (ICU) were not included. The prescriptions having more than one drug were evaluated. DDIs where the drugs commonly used in combination for beneficial therapeutic effect and those identified upon discontinuation of one of the agents were also excluded.

Gathering evidence about DDIs

The evidences about identified DDIs were gathered in stage II. The references cited for each DDIs in compendia were reviewed. The assembled literature for each DDI was examined by two authors (SD and SA). The evidence report was prepared for all DDIs. Another author (BK) verified the adequateness of each evidence report. After verification, the reports were sent to an expert panel for review.

Evaluation of candidate DDIs

At stage III, the clinically relevant and well-supported DDIs were focused on for future reference and intervention. A document containing a summary and bibliography of each interaction along with the copies of the key articles were submitted to the expert panel. The interaction types were classified into major, moderate, and minor. The classifications below are used as a guideline.

Major	Clinically significant interactions where the risks outweigh beneficial effects. Suggestion - avoid combinations
Moderate	Reasonably clinically significant interactions Suggestion- avoid or use only under special conditions.
Minor	Nominally clinically significant where the drugs can be Suggestion- use after assessing risk with monitoring, take counteracting steps with proper counseling

RESULTS

A systematic evaluation of the literature and an expert-panel process were used for the identification of clinically important DDIs. The number of drugs prescribed in the sample was 4.15 on average ranging from 2 to 11 drugs. A total of 2006 medicines were prescribed in 483 prescriptions. DDIs were found in 21.53% prescriptions (n=104). The panel evaluated 168 DDIs amongst all the assessed prescriptions. The types of interactions among those were found to be major 32 (19%), moderate 85 (51%), and minor 51(30%) (Figure 1).

Table 1 enlists the number of interactions identified in each compendium. The candidate DDIs were then cross-referenced to each other to evaluate total DDIs of different types. After all considerations, the expert panel decided to exclude therapeutically beneficial combinations and concluded 13 DDIs as

Table 1: Interactions listed by drug interaction compendia

SN	Compendia	Interactions (n)
1	MICROMEDEX DRUG-REAX	105
2	Evaluation of Drug Interactions	115
3	Drug Interaction Facts	85
4	Drug Interactions: Analysis and Management	52

Table 2: DDIs selected by the panel as having the greatest clinical importance

SN	Object drug	Precipitant drug	Likely Hazards
1	Atorvastatin	Azithromycin	Muscles toxicity
2	Clopidogrel	Omeprazole	Reduced efficacy in heart attack or stroke prevention
3	Levofloxacin	Prednisolone	Tendinitis
4	Warfarin	Metronidazole	Bleeding complications
5	Enalapril	Allopurinol	Anaphylaxis and myocardial infarction
6	Metformin	Enalapril	Hypoglycemia
7	Furosemide	Tizanidine	Hypotension
8	Metoprolol	Theophylline	Breathing problems
9	Methotrexate	Omeprazole	Methotrexate toxicity
10	Methotrexate	Pantoprazole	Methotrexate toxicity
11	Insulin	Ciprofloxacin	Hypoglycemia
12	Warfarin	Diclofenac	Bleeding complications
13	Losartan	Spirono-lactone	Hyperkalemia

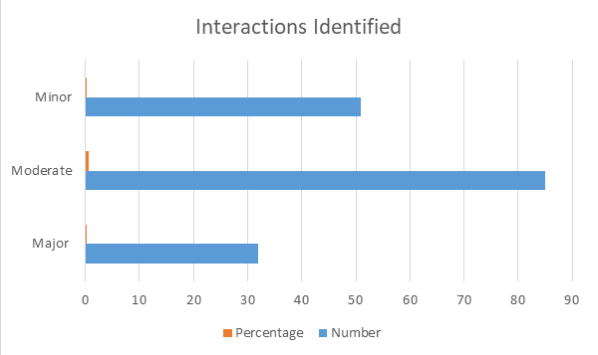

Figure 1: Number and percentage of types of interactions identified

clinically relevant (Table 2). Most of the interacting agents of clinically relevant DDIs were found to be drugs acting on the cardiovascular system (Atorvastatin, Clopidogrel, Warfarin, Enalapril, Furosemide, Metoprolol, Losartan, and Spironolactone) followed by antibiotics (Azithromycin, Ciprofloxacin, and Levofloxacin), proton pump inhibitors (Omeprazole and Pantoprazole), drugs acting on the musculoskeletal system (Diclofenac, Allopurinol, and Tizanidine), anti-diabetic agents (Metformin and Insulin), antimetabolites (Methotrexate), steroid (Prednisolone), and bronchodilator (Theophylline).

DISCUSSION

Based on this study, among several subsets of interacting drug combinations, the expert panel concluded 13 interactions to be more common and clinically relevant. A similar study conducted in the United States concluded 25 interactions as a clinically important and possible to occur in community and ambulatory pharmacy settings.[13] The types of interactions observed in our study were major 32 (19%), moderate 85 (51%), and minor 51(30%). DDIs were found in 21.53% of the total prescription samples, which somehow coincides with a study conducted in Bharatpur District Hospital, Nepal where it was 19.1%.[14] However, the result varies considerably with the findings of a study conducted in a tertiary care teaching hospital of Gujarat, India where it was 71.50%.[15]

Drug interaction compendia include a large number of drug interactions. However, these references may differ significantly. As DDI compendia seem to be dependent on a few authors or a small number of editors to evaluate drug interactions, consistent results related to DDIs demands great effort.[16] Likewise, drug manufacturers have become increasingly careful in the identification and reporting of DDIs.[13] Automated system of computerized drug interaction screening is useful for rational use of drugs.[17] It is used widely for identifying and reducing the possible harmful interactions, however, results of computer systems also differ greatly, to which drug interactions trigger warnings.[6] Despite the numerous advantages of information technology, drawbacks such as insufficient patient data and inappropriate medical reasoning may sometimes make the identification of drug interaction difficult. Practitioners' alignment with the traditional way and feeling less comfortable with the automated systems may be another barrier in information technology innovations for rational drug use.[18] Many prescribing decisions are made by physicians based upon individual patient characteristics, disease state, and various economic and social factors[19,20] which may be hard to manage solely by relying on computer software.[21]

The automated prescribing systems with sufficient data to support medical reasoning could be a better solution to reduce the medication errors.[22] Such system links to different information such as patients' medication history, interactions and ADR alerts, formulary drugs, standard treatment guidelines inform prescribers instantly to a correct therapeutic regimen with proper accessory information.[23] The objective of our study was to identify DDIs to make healthcare practitioners such as physicians, pharmacologists, pharmacists, and nurses vigilant about such events.

Though DDIs have become a serious problem due to the availability of potent drugs and poly-pharmacy practice, many drug interactions can be predicted and prevented.[24] DDIs cause failure of therapy leading to severe harm to the patients. But, the interactions can be used in therapeutics with proper monitoring for benificial effects as well. The critical judgment of clinical staff and patient compliance are essential in this regard. However, it is better to have no DDIs in therapy.

Therefore, to prevent DDIs, close monitoring is required in susceptible patients and in patients taking multiple drug therapy. DDIs can be recognized by maintaining patient medication history and checking the interactions based on the existing literature and automated software. Healthcare practitioners should be on the lookout for the timely recognition and prevention of DDIs.[25] Thus, the drug interaction monitoring programs are required to set up in healthcare setting. Such programs detect the drug interactions occurring in the healthcare setting, develop intervention

approaches, and assess the impact of the interaction.

The intervention strategies may include discussion among the peers, the drug and therapeutics committee members, and also with overall healthcare professionals. Giving alternative drugs that may cause major interactions or adding drugs that counteract the toxic effects of another drug or changing the dose or making adequate time gap between administrations of drugs with interacting potential also may be of help.[26] Being aware of the drugs being used and avoiding unnecessary drug therapy is a must to prevent interactions.[24]

Limitations: Based on the best evidence available, subjective judgments are made by the expert panels. The results may be dependent on the judgments of members of an expert panel. These interactions represent a selected set of all probable DDIs. Though the identified DDIs in this study were for the hospital setting only, other clinically important DDIs should also be identified and prevented depending on the setting and nature of drugs.

The patient-specific relevance of a particular drug interaction is tough to determine referring to the tool used in this study alone given the large number of variables that may apply.

We did not exclude prescriptions from other departments in case of patients' multiple OPD visits along with MOPD. In such a case, drugs prescribed from one department can interact with drugs prescribed from another department for the same patient.

All the drug-reference books or information resources containing information related to DDIs were not consulted. The compendia most commonly used by healthcare professionals to determine DDIs were referred. Lastly, the systematic evaluation of health outcomes and expenditures associated with the 13 DDIs considered clinically relevant are not performed.

CONCLUSION

The drug interactions are identified by a panel of experts using a standard evaluation tool. These represent a category of interactions acclaimed by drug interaction compendia and are considered to be clinically important and likely to occur in clinical settings. Clinically significant DDIs can be preventable and can also be used for the beneficial effects in MTM in clinical settings based on the critical judgment of clinical staff and patient compliance. Based on the findings, we suggest different departments to check drugs prescribed by other departments in case of patients' multiple OPD visits. We encourage healthcare practitioners to prevent patients from taking these interacting medications and use an automated system to focus interaction alerts on such and other important DDIs. Ample knowledge regarding DDIs, the inclusion of automated system in prescribing and dispensing, and inter-professional collaboration of a clinical team are liable to prevent and manage such events and help in rational drug therapy.

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