SHORT COMMUNICATION

Possible drug-drug interactions in the prescriptions of discharged patients at National Hospital Sri Lanka in Colombo

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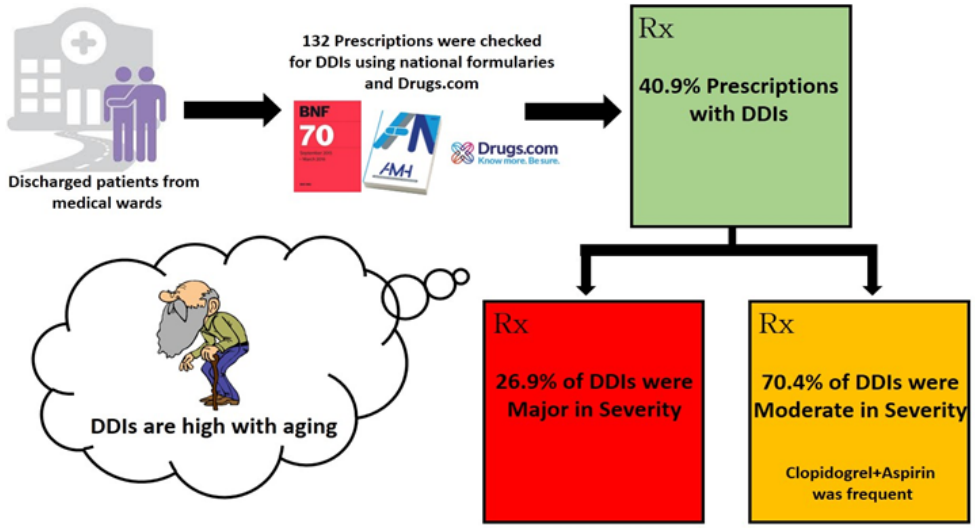

Highlights

- Prevalence of possible Drug-Drug Interactions (DDIs) in discharged prescriptions were 40.9%.
- Majority (70.4%) of DDIs were moderate in severity.
- Most frequently appeared drug-drug interaction in discharged prescriptions was Clopidogrel and Aspirin combination which is a moderately sever.
- There is a relationship between age and the presence of possible DDIs.

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Possible drug-drug interactions in the prescriptions of discharged patients at National Hospital Sri Lanka in Colombo

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Abstract: Drug-Drug Interactions (DDIs) can be defined as an alteration of the desired therapeutic response of one drug by another drug when two or more drugs are administered simultaneously. A descriptive cross-sectional study was carried out in ten randomly selected medical wards at the Colombo National Hospital, Sri Lanka. Discharged prescriptions (132) were examined using software; Drugs.com, and National Formularies (British National Formulary, Australian Medicine Handbook) for DDIs. Out of 132 discharged prescriptions, 41.6% were detected with possible DDIs. Out of the total found interactions, 16.4% were major and 83.6% were moderate (in 46 prescriptions) as per the severity level in the above Formularies. The most frequent (n = 24) DDI was between Clopidogrel and Aspirin with a moderate severity level. Major DDIs were reported with Furosemide + Amiodarone (n = 06) and Losartan + Amlodipine (n = 6). There was a significant relationship between the age and the presence of DDIs in discharged prescriptions ($p = 0.0341$). The prevalence of possible DDIs in the discharged prescription of elderly people needs to be considered even with the significant absence of major DDI as per the study. More emphasis on the DDI detection process in discharged prescriptions could improve medication safety and prevent medication-associated hospital readmissions.

Keywords: Drug-Drug interactions; discharged prescriptions; DDIs; medical wards; clopidogrel.

INTRODUCTION

Drug-Drug Interaction (DDI) is one of the common types of medication errors in developed countries, particularly in the elderly population due to concurrent use of two or more drugs (WHO, 2016). The prevalence of patients with DDIs in-hospital healthcare worldwide seems to be between 15 – 45% (Cruciol and Thomson, 2006). One drug can alter the therapeutic outcome of another drug commonly during simultaneous administration. The effect can be synergism or antagonism or idiosyncratic (Kumar and Clark, 2009). Early detection of DDIs before the drugs reach the patient would prevent unwanted consequences. In practice, clinically important DDIs are more common with drugs that, (a) have a steep dose-response curve and a narrow therapeutic index, (b) are known hepatic enzyme inducers or inhibitors, and (c) exhibit saturable metabolism and with long-term use.

DDIs can be divided into two types as pharmacodynamic interactions and pharmacokinetic interactions. Pharmacodynamic interactions involve the actions of both drugs in the same target site, exerting synergism or antagonism. Pharmacokinetic interactions involve alteration of plasma concentration of one drug by another, changing the amount of drug at the target site resulting in an altered clinical effect (Brown and Bennett, 2003).

According to previous studies, there is a correlation between potentially dangerous drug interactions and the number of co-administered drugs. Therefore, it is crucial to consider the number of drugs when prescribing (Geppert *et al*., 2003). Cruciol and Thomson (2006) showed that medical specialty and number of prescribers presented significant differences in DDI prevalence. Another important risk factor that can give rise to DDIs is polypharmacy. Polypharmacy is the concurrent use of multiple medications by one individual (Duerden *et al*., 2013). Polypharmacy is usually defined as the use of five or more drugs (Hilmer, 2008). Elderly patients exposed to polypharmacy should be closely monitored as they are at increased risk of clinically significant drug interactions. A study conducted by Bjerrum and coworkers showed that 25% and 36% received drugs carrying the risk of interaction in the age groups of 60 – 79 years and over 80 years, respectively, due to polypharmacy. Among those individuals exposed to potential drug interactions, 62% were exposed to only one drug interaction and 38% to two or more different drug interactions (Bjerrum *et al*., 2003). They further revealed that DDIs also depend on the type of drug prescribed. Diuretics, NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), ACE-inhibitors (Angiotensin Converting Enzyme inhibitors), digoxin, oral antidiabetics, calcium channel blockers, anticoagulants, and beta-blockers were found to be accountable for a higher number of potential interactions. When focusing only on major drug interactions, potassium-sparing diuretics and oral anticoagulants were the most frequently involved drugs (Bjerrum *et al*., 2003). Costa (1991), Gosney and Tallis (1984) and Manchon *et al*. (1989) have shown that approximately 37 – 60% of patients admitted to hospital may have one or more potentially interacting drug combinations at admission. During hospitalization new drugs are added to the drug regimen due to severe and multiple diseases, and this increase potentially interacting drug combinations (Kulkarni *et al*., 2013). According

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to a study done on patients at discharge in a hospital in Switzerland, out of 747 potential DDIs, 402 (53.8%) were new at the time of discharge due to a change of the medication during the hospital stay (Egger *et al*., 2003). From a total of 1014 prescriptions collected from hospital and community pharmacies of different areas of Karachchi, 40% had at least one interacting combination with 13% major, 17% moderate, and 10% minor interactions (Kafeel *et al*., 2014). A severity assessment in a study on DDIs through prescription analysis in a South Indian teaching hospital shows that majority of the DDIs were moderate (70%) followed by minor (28%). The study results showed that as the number of drugs increases in a prescription, the number of DDIs also increases. Furthermore, it has been found that most of the DDIs were pharmacokinetic drug interactions (42%) and 34% unknown mechanisms and 24 % from pharmacodynamic mechanisms. The findings of the study showed that the prescriptions for cardiovascular with respiratory disease conditions had the greatest number of drug interactions on average (Kulkarni *et al*., 2013).

There are limited studies reported in Sri Lanka on this topic causing a gap in the knowledge of DDIs. A study on drug-related problems in two government hospitals of Sri Lanka has revealed that 13% of drug-related problems comprise of DDIs (Dorabawila and Mamunuwa, 2014). Therefore, this study was directed to bridge the gap and to provide information on the prevalence of possible DDIs which ultimately targeted to provide knowledge to responsible parties, to ensure patient safety and quality of the healthcare system.

MATERIALS AND METHODS

A quantitative, descriptive, and observational study was carried out in ten (10) medical wards of the Colombo National Hospital of Sri Lanka from March 2018 to June 2018 and all patients discharged from there were considered as the study population. Both male and female patients above 18 years old and patients with at least two drugs in the discharged prescription were included in the study. Patients who were discharged (a) against the medical recommendations, (b) to transfer into another healthcare institute, and (c) with prescriptions of herbal medicine and food supplements were excluded.

The sample size was calculated using an online sample size calculator (Raosoft) considering a 5% margin of error and 95% confidence interval using available discharge statistical data at the hospital. A convenience sampling technique was used in achieving the calculated sample size. Pretested in-house data extraction sheet was used to collect data from discharge prescriptions (through observation) and analyzed descriptively and inferentially using Statistical Package for the Social Sciences (SPSS) software version 21. Preliminary detection of drug interaction was done by using software (Micromedex, Drugs.com). Then the confirmation and further analysis were done by using National Formularies (British National Formulary and Australian Medicine Handbook).

Ethical approval for the study was obtained from the Ethics Review Committee of the Colombo National Hospital of Sri Lanka (NHSL). Permission to conduct the research was obtained from the Deputy Director-General of Colombo NHSL and the consultants of each ward. Written informed consent was taken from the patients and confidentiality of data was maintained.

RESULTS AND DISCUSSION

Demographic and clinical characteristics of the patients

This study analyzed 132 discharged prescriptions. A majority (81.1%) of the prescriptions belonged to female patients. If the age is considered, most of the patients were more than 51 years old (72.6%). Most (96.2%) of the discharged patients were married. The ethnicity and educational levels of the respondents are shown in Table 1.

Table 1: Demographic characteristics of patients on discharged prescription.

Demographic Character	Frequency (N)	Percentage (%)
Age (Years)		
18 – 25	00	0
26 – 35	06	4.5
36 – 50	30	22.7
51 – 65	48	36.3
> 65	48	36.3
Gender		
Male	25	18.9
Female	107	81.1
Ethnicity		
Sinhala	81	61.4
Tamil	13	9.8
Muslim	38	28.8
Other	00	0
Marital Status		
Single	05	3.7
Married	127	96.2
Educational Level		
None	18	13.6
Up To O/L	99	75
Up To A/L	10	7.6
Graduate	05	3.8
Postgraduate	00	0

When considering the clinical characteristics, a majority (88.6%, n = 117) of the discharged patients had a past medical history where 43.6% of them were with cardiovascular disease (Table 2) and 63.2% of the patients had regular clinic visits to the NHSL.

Prevalence of drug-drug interaction and common combinations of drugs in interactions

Out of the 132 discharged prescriptions considered during the study, possible drug-drug interactions were detected in 55 prescriptions after analyzing a total of 705 drugs. The percentage of the presence of drug-drug interactions was 41.6%. Possible 78 instances of drug-drug interactions were detected on the above prescriptions and the average presence of drug-drug interactions per prescription was 0.6. The average number of drugs per prescription was 5.3. There was no relationship between the number of drugs and the presence of DDI (p = 0.0423). This finding is not aligned with the finding of the study of Geppert *et al*. (2003). The maximum number of drug-drug interactions per prescription was seven out of nine drugs on the prescription.

Table 2: Diseases on past medical history

Disease on Past Medical History	Frequency (N)	Percentage (%)
Diseases of Cardio vascular System	51	43.6
Diseases of Endocrine System	6	4.5
Diseases of Nervous System	6	4.5
Diseases of Digestive System	5	4.3
Diseases of Respiratory System	5	4.3
Disease of Kidney	7	6.0
Combination of Diseases	37	31.6
Cardiovascular + Endocrine	27	
Cardiovascular +Endocrine +Neurological	2	
Cardiovascular +Neurological +Respiratory	3	
Other Combinations	*5*	
Total	117	100%

Table 3: Degree of possible drug-drug interaction

Degree of Possible Drug-Drug Interactions	Number of Interacting Drug Pairs	Number of Prescriptions with Interaction
Major	07	9
Moderate	09	46

Out of all the prescriptions with drug-drug interactions, only a few prescriptions (n = 9) had major interactions and most of the prescriptions had moderate interactions (Table 3). This is consistent with the findings of the studies of Egger *et al.* (2003) and Chelkeba *et al.* (2013).

Out of total interactions, 16.4% of interactions were major and 83.6% were moderate. The most frequently appeared drug-drug interaction in discharged prescriptions was Clopidogrel and Aspirin combination which is moderate in severity (Table 4). The combinations Frusemide and Amiodarone, Losartan and Amlodipine, Clarithromycin and Atorvastatin/Simvastatin also appeared in relatively high frequencies in discharged prescriptions.

Out of the total number of patients, 41.6% of discharged patients were found to be having possible drug-drug interactions (DDIs) in their prescriptions. The prevalence of occurrence of DDIs is much lower compared to studies done in other developing countries such as India which is a good sign (Kulkarni *et al*., 2013). Most of the DDIs were moderate and similar results were reported from studies of other countries (Kulkarni *et al*., 2013, Salwe *et al*., 2016).

Drugs that account for the highest number of interactions revealed by this study include NSAIDs, anticoagulants, Beta-blockers, Calcium channel blockers, ACE inhibitors, oral antidiabetics, and diuretics. Similar results were reported in a study conducted in Denmark with a primary health care facility (Bjerrum *et al*., 2003). There was no relationship between gender and the presence of drug-drug interaction (p = 0.0546) but there was a relationship between the age and presence of DDT in discharged prescription (p = 0.0341). The prevalence of possible DDIs in the discharged prescription of elderly people needs to be considered even with the significant absence of major DDI as per the study. More emphasis on the DDI detecting process in discharged prescriptions could improve medication safety and prevent medication-associated hospital readmissions.

CONCLUSION

The prevalence of DDIs in discharged prescriptions was 40.9% and the majority (70.4%) were moderate in severity. The most frequently appeared DDI in discharged prescriptions was Clopidogrel and Aspirin combination which is moderate in severity. NSAIDs, anticoagulants, Beta-blockers, Calcium channel blockers, ACE inhibitors, oral antidiabetics, Angiotensin receptor Blockers, and diuretics were prominently found in interacted drug combinations. There was no relationship between gender and the presence of possible drug interaction, but age and the presence of possible drug-drug interaction have a relationship.

However, a thorough assessment of the patient's condition and prescribed drug doses need to be considered to assess the potential severity of these interactions to the patient which was the main limitation of this study. Thus, the findings of this research can be taken as a pilot study, and it is recommended to enhance awareness of the prevalence of drug interactions among health care professionals. Furthermore, direct studies should be conducted on

Table 4: Combination of drugs with possible drug-drug interactions

Interacting Drug Pair	Type of Interaction	Mechanism of Interaction	Frequency
Clarithromycin + Theophylline	Major	Clarithromycin inhibits metabolism of theophylline	02
Clopidogrel + Aspirin	Moderate	Increased risk of bleeding	24
Clarithromycin + Atorvastatin/ Simvastatin	Major	Clarithromycin increase plasma concentration and increased risk of myopathy	07
Tramadol + Domperidone	Moderate	Tramadol antagonise effects of domperidone on gastro-intestinal activity	02
Losartan + Carvedilol	Moderate	Enhanced hypotensive effect	06
Gliclazide + Carvedilol	Moderate	Warning signs of hypoglycaemia (such as tremor) with gliclazide may be masked	03
Metoprolol + Sildenafil	Moderate	Sildenafil increases hypotensive effect of metoprolol.	01
Enalapril + Metformin	Moderate	Hypoglycaemic effect of metformin is enhanced	10
Aspirin + Losartan	Moderate	Aspirin reduce the hypotensive effect of losartan	06
Aspirin + Spironolactone	Moderate	Aspirin antagonises diuretic effect of Spironolactone	01
Spironolactone + Losartan	Major	Enhanced hypotensive effect and increased risk of hyperkalaemia	01
Spironolactone + Prazosin	Major	Increased risk of first-dose hypotension	01
Frusemide + Prazosin	Major	Increased risk of first-dose hypotension	01
Gliclazide + Frusemide	Moderate	Frusemide antagonise hypoglycaemic effect of gliclazide	01
Frusemide + Amiodarone	Major	hypokalaemia caused by frusemide causes increases cardiac toxicity	06
Losartan + Amlodipine	Major	Enhanced hypotensive effect	06

drug interactions to identify methods to minimize them. Expanding the pharmacist role in medication review can be crucial in the prevention of DDIs.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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