Assessment of Potential Drug-Drug Interactions among Patients with Diabetes Mellitus and Hypertension

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ABSTRACT

Introduction: Drug-drug interactions arising from polypharmacy in patients with chronic multiple comorbid conditions is one of the most important risk factors for development of adverse drug outcomes. Therefore, it is important for early detection and management of potential drug-drug interactions (pDDIs). This study aims to identify and manage the pDDIs in patients with diabetes mellitus and hypertension.

Materials and methods: This cross-sectional study was conducted over a period of three months at general medicine wards of a secondary care hospital. The medication charts of the eligible patients were reviewed to identify the pDDIs using Medscape Drug Interaction Checker. The details related to identified pDDIs, such as type, severity and outcome were documented. The collected data was analyzed following descriptive statistics.

Results: A total of forty patients were enrolled in the study. A total of 145 medications were used in 409 episodes. The mean ± SD number of medications used were 10.2 ± 3.0 per patient. A total of 190 pDDIs were identified involving 121 interacting drug-pairs in 37 patients. The median (IQR) number of pDDIs were 4 (2.5-8) per patient. The highest number of pDDIs documented were 13 in one patient. Ondansetron + Metformin was the most frequent (8/190, 4.2%) interacting drug-pair documented. There were seven pDDIs identified with serious severity (3.6%) and in five occasions the pharmacotherapy was changed.

Conclusion: The frequency of pDDIs was high in patients diagnosed with both diabetes mellitus and hypertension. The healthcare providers must be vigilant in early detection and management of these pDDIs.

Keywords: Diabetes Mellitus, Hypertension, Multiple Comorbid Conditions, Polypharmacy, Potential Drug-Drug Interactions.

INTRODUCTION

A drug-drug interaction may result in an increased action of one or more drugs leading to adverse drug outcomes or decreased efficacy of one or more drugs leading to treatment failure.[1, 2] Polypharmacy, because of multimorbidity is the one of the most crucial factors that increases the risk of drug-drug interactions. In addition, drug-drug interactions are the most important cause of many preventable adverse drug outcomes especially in elderly.[3, 4] Untreated and/or undertreated chronic conditions such as diabetes mellitus and hypertension increase the risk for development of complications. To avoid these complications and better manage the clinical conditions, multiple medications are used frequently.[5, 6] However, use of multiple medications or polypharmacy is often a double-edged sword that increases the risk of potential drug-drug interactions (pDDIs), while adequately managing diabetes mellitus, hypertension, and related complications. Therefore, it is important to identify and manage pDDIs in patients with chronic and multimorbid conditions such as diabetes mellitus and hypertension. The main objective of this study was to identify the frequency of pDDIs among hospitalized patients with diabetes mellitus and hypertension.

MATERIALS AND METHODS

This cross-sectional study was conducted over a period of three months between August and October 2024, at general medicine wards of a secondary care hospital in Bengaluru, Karnataka, India. The ethical approval was obtained by the institutional ethics committee of the secondary care hospital (Ref. No.: NCP/HEC/-CERT-004/2024). All the adult patients who admitted to the general medical wards of the study site with diagnosis of hypertension and/or diabetes mellitus or both, with and without other comorbidities were enrolled after obtaining their informed consent. The patients were followed from the day of admission till discharge. The demographic details (age and sex) and the clinical details (reason for admission, diagnosis, medications used, dose, frequency, and duration) were captured using a standard data collection form designed for the study. The patients' medication chart was reviewed and screened for presence of potential drug-drug interactions, if any, using Medscape Drug Interaction Checker.[7] The details related to identified

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pDDIs, such as type (pharmacokinetic or pharmacodynamic), severity (contraindicated, serious, significant, and minor) and outcome were documented.

STATISTICAL ANALYSIS

Descriptive statistics (frequency and percentage) was applied to present the demographic and clinical data. Median and interquartile range (IQR) was used to present the age distribution, diagnoses, and frequency of pDDIs whereas, mean and standard deviation was used to present the frequency of medication use among the study population. The type and severity of identified pDDIs were presented as frequency and percentages. All the study data was analyzed using JMP version 17 statistical software.

RESULTS

A total of forty patients were enrolled in the study. Most of the patients were males (26, 65%). The median (IQR) age of the study participants was 67 (55-75) years and most of the patients were belonging to the age group of 71-80 years (13, 32.5%), followed by 51-60 years (25%). The median (IQR) number of diagnoses were 3 (2-4). Most of the patients were having both hypertension and diabetes with other comorbidities (21, 52.5%). The demographic and clinical details of the study participants are presented in Table 1.

A total of 145 medications were used in 409 episodes among forty patients. The mean ±SD number of medications used were 10.2 ± 3.0 per patient. Pantoprazole (29/40, 72.5%) was the most frequent medication used followed by ondansetron (16/40, 40%). The list of 10 most frequent medications used among the study population are presented in Table 2.

Among forty patients, three patients did not have any pDDIs. A total of 190 pDDIs were identified involving 121 interacting drug-pairs in 37 patients. The median (IQR) number of pDDIs were 4 (2.5-8) per patient. The highest number of pDDIs documented were 13 in one patient. The number of pDDIs with number of patients are presented in Table 3 and Table 4 provides the list of ten most frequent interacting drug-pairs.

Most of the identified pDDIs were pharmacodynamic interactions (155, 81.5%), followed by pharmacokinetic interactions (29, 15.2%) and six (3.1%) were with unspecified mechanisms. Most of the interactions were belonging to the severity category of monitor closely (128, 67.3%), followed by minor (55, 28.9%) and seven (3.6%) were serious in severity. As a precautionary measure, among seven pDDIs with serious severity, in five occasions the pharmacotherapy was changed. The details are presented in Table 5.

DISCUSSION

Diabetes mellitus and hypertension are the most common non-communicable clinical conditions observed.[8, 9] In addition, when a patient is diagnosed with either of these clinical conditions, there are certain medications that are used for primary prevention or sometimes patients may be having a comorbid condition that necessitates use of multiple drugs. Presence of multiple comorbidities is directly related to use of multiple medications and hence increased chances of drug-drug interactions.[10] This study focused on identification and management of such drug-drug interactions and their complications among patients diagnosed with diabetes mellitus and/or hypertension and with or without comorbidities.

In this study most of the patients were above the age of fifty years (33/40, 82.5%) and most of the patients were suffering from more than two clinical conditions (25/40, 62.5%). More than half of the study population were suffering from diabetes mellitus and hypertension along with other clinical condition (21/40, 52.5%). This is the reason for use of multiple medications in our study (10.2 ± 3.0 per patient) and is the single most factor for a high number of pDDIs identified among the study population (Median: 4, IQR: 2.5-8).

A study conducted in Nepal reported the frequency of drug-drug interactions as 44.1% among diabetic patients.[11]

Demographic parameter	Category	Number	Percentage
Sex	Male	26	65
	Female	14	35
Age group	41-50 years	07	17.5
	51-60 years	10	25
	61-70 years	06	15
	71-80 years	13	32.5
	81-90 years	04	10
Median (IQR) age		67 (55-75) years	
No. of diagnoses	2	15	37.5
	3	13	32.5
	4	7	17.5
	5	4	10
	7	1	2.5
Median (IQR) diagnoses		3 (2-4)	
Diagnoses	Hypertension + Diabetes mellitus with other clinical condition	21	52.5
	Diabetes mellitus with other clinical condition	11	27.5
	Hypertension with other clinical condition	08	20

Table-1: Demographic and clinical details of the study participants (N=40)

Whereas a study conducted in India reported the frequency of pDDIs among hypertensive patients as 48%.[12] In contrast, the frequency of pDDIs was higher, rather double in our study (37/40, 92.5%). This difference could be because of including patients with multiple comorbidities in our study as compared to these studies that included patients with only diabetes mellitus and only hypertension. Our study also evidences the highest number of pDDIs was 13 in one patient who had multiple comorbidities. This observation also strengthens the theory of increased comorbidities with increased risk of pDDIs.[13]

S. No.	Name of the medication	Frequency	Percentage
1	Pantoprazole	29	72.5
2	Ondansetron	16	40
3	Insulin	14	35
4	Metformin	14	35
5	Acetaminophen	12	30
6	Normal saline	12	30
7	Aspirin	9	22.5
8	Levetiracetam	9	22.5
9	Ceftriaxone	8	20
10	Ipratropium bromide	8	20

Table-2: Ten most frequently used medications among the study population.

Number of pDDIs	Number of patients	Total number of pDDIs
1	8	08
2	1	02
3	5	15
4	5	20
5	2	10
6	2	12
7	4	28
8	5	40
9	1	09
10	1	10
11	1	11
12	1	12
13	1	13
Total	37	190

Table-3: Distribution of pDDIs among study population.

In our study, the top ten interacting drug-pairs included most of the antidiabetic medications as compared to antihypertensive medications (metformin and insulin). The similar observations were reported by Tuladhar LR et al.[11] Telmisartan and metoprolol were the common antihypertensive medications involved in the pDDIs in our study. Similar observations were reported in a study conducted by Sivva D et al.[14] In our study, most of the study population were diagnosed with both diabetes mellitus and hypertension, and were prescribed with aspirin for primary prevention, which is another most common medication implicated in the top ten pDDIs. The highest number of drug-drug interactions involving aspirin was reported among patients with diabetes mellitus and hypertension in studies conducted in Malaysia[15] and in India[12], which is very much similar to our study findings.

Majority of the pDDIs were belonging to severity category of monitor closely (67.3%) and 28.9% were minor in severity, for which no action was taken, however patients were followed until discharge. A study conducted by Subramanian A also reported that majority of the pDDIs were minor (14.6%) and significant (85.4%), which is comparable with our study findings.[12] In our study there were seven patients with serious pDDIs, of which five patients were managed with change in pharmacotherapy, and rest two were monitored as there was a little clinical significance. A study by Sankar V et al. reported similar results, in which they observed ten pDDIs with serious severity category among diabetic patients.[16] It was interesting to note that among seven pDDIs with serious

S. No.	Interacting drug-pairs	Frequency	Percentage
1	Ondansetron + Metformin	8	4.2
2	Pantoprazole + Budesonide	6	3.2
3	Budesonide + Metformin	5	2.6
4	Aspirin + Clopidogrel	4	2.1
5	Aspirin + Enoxaparin	4	2.1
6	Furosemide + Metformin	4	2.1
7	Metoprolol + Telmisartan	4	2.1
8	Potassium citrate + Insulin	4	2.1
9	Telmisartan + Insulin	4	2.1
10	Aspirin + Metoprolol	3	1.6

Table-4: List of ten most frequent interacting drug-pairs among the study population.

S. No.	Interacting drug-pair	Outcome of interaction	Management
1	Azithromycin + Ondansetron	Both increase QTc interval	Azithromycin was replaced by amoxicillin
2	Azithromycin + Ondansetron	Both increase QTc interval	Azithromycin was replaced by amoxicillin
3	Donepezil + Ondansetron	Both increase QTc interval	Ondansetron was stopped
4	Rifampicin + Budesonide	Rifampicin decreases the level or effect of budesonide by affecting hepatic/intestinal enzyme CYP3A4 metabolism	No action was taken as budesonide was given through nebulization
5	Rifampicin + Isoniazid	Rifampicin increases toxicity of isoniazid by increasing metabolism	No action was taken however, liver function tests were monitored
6	Ciprofloxacin + Ondansetron	Both increase QTc interval	Ciprofloxacin was replaced by amoxicillin
7	Morphine + Prasugrel	Morphine decreases the level or effect of prasugrel by inhibition of GI absorption	Prasugrel was replaced by aspirin

Table-5: Details of pDDIs with serious severity identified among the study population.

severity four were due to use of ondansetron. Ondansetron is one of the most widely used antiemetic agent belonging to the class of serotonin 5-HT_3 receptor antagonists.[17] It interacts with most of the medications because of its effect on serotonin due which the Food and Drug Administration had issued a warning, to be cautious while using ondansetron.[18]

CONCLUSION

The frequency of pDDIs was high in patients diagnosed with both diabetes mellitus and hypertension as compared to patients with diabetes mellitus alone or hypertension alone. In addition, the risk of pDDIs increases in patients with additional acute clinical conditions due to added multiple drug therapy. Therefore, healthcare providers must be vigilant in early detection and management of these pDDIs, that will help in preventing adverse drug outcomes and achieving positive therapeutic outcomes in these special population.

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