Drug - Drug Interactions among Chronic Kidney Disease patients in a tertiary hospital.

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Abstract

Background: Drug interaction (more precisely 'drug-drug interaction') refers to modifying the action of one drug by another when administered simultaneously or in quick succession. Chronic Kidney Disease (CKD) patients often require polypharmacy, which puts them at the risk of the developing Drug - Drug Interactions (DDIs) and various adverse reactions. Not all patients taking interacting drugs experience adverse consequences, but it is advisable to take due precautions to avoid mishaps in all cases where interactions are possible. Hence, this study was undertaken to identify the DDIs among the drugs prescribed to CKD patients.

Materials and methods: A Cross-sectional study was conducted in the Department of Nephrology. A total of 80 patients with CKD were included. Patients with CKD with other comorbid conditions, CKD patients of either sex above the age group of 18 years were included. LEXICOMP drug interaction software was used for potential DDI (pDDI) identification.

Results: Patients mean age was 47.24±14.37 years with male predominance of 72.5 %. A total of 604 drugs were prescribed with a mean of 7.55 ± 2.73. The most common medications prescribed was Amlodipine (6.3%). DDIs were identified in 74 patients. 46 showed 1 to 5 pDDIs, 22 patients showed 6 to 10 p DDIs, 4 patients showed 11 - 15 DDIs, and 2 patients showed 16 to 20 pDDIs. According to the Lexicomp severity classification, 270 were Type C, 57 were Type D & 55 were Type B.

Conclusion: The recognition of potential DDI and key combinations of drugs avoids treatment failure situations or minimizes drug toxicity.

Keywords: Chronic Kidney disease, drug-drug interaction, Co-morbidities, Medication

Introduction

Drug interaction (more precisely 'drug-drug interaction') refers to modifying the action of one drug by another when administered simultaneously or in quick succession. The mode of drug modification is mainly of quantitative nature, for example - enhanced or diminished intensity response. Occasionally, it may be qualitative, like an abnormal or different response type may be observed. These interactions often occur either at the pharmacokinetic or pharmacodynamic level or by some other mechanisms.[1]

In clinical practice, most of the time treating patients with chronic diseases, multiple drugs are often combined. There may be Drug-Drug Interactions (DDIs), some may have beneficial effects like the synergistic activity, and in some instances, there could be undesired and harmful effects, such as ineffective treatment and severe adverse events leading to increased morbidity, which in turn may lead to increased duration of hospital stay and increased cost of medical care, which produce burden to the patient[1].

In reality, the reporting and documenting of these DDIs are scarce, but knowledge of different drugs' pharmacodynamic and pharmacokinetic properties suggests the potential risks connected to drug interactions. The occurrence of these potential DDIs in patients may be prevented by proper vigilance and understanding of these interactions in vivo. For this purpose, the identification and classification of drug interactions may help us to anticipate and prevent them clinically. These DDIs become more frequent in patients who suffer from long-standing illnesses commonly associated with various co morbidities

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and age-related health issues like impaired hepatic metabolism and decreased renal function requiring multiple medications. Chronic kidney disease (CKD) patients often require poly-pharmacy, which puts them at the risk of the developing DDIs and various adverse reactions[2].

The kidneys play a prominent role in maintaining the body's homeostasis and regulates the excretory and endocrine functions[2]. Medical care for CKD patients is complex due to widespread comorbidities and significant risk factors for CKD. The progression of CKD and kidney function deterioration from stage 1 to stage 5 can be slowed by optimal treatment of underlying comorbidities and risk factors[2].

Hypertension, Diabetes mellitus, Anaemia, Electrolyte abnormalities, Cardiovascular disease, and left ventricular hypertrophy are highly prevalent in CKD patients. The proper management of comorbid conditions is vital in retarding the progression of CKD and reducing mortality. This leads to the usage of several medications to manage CKD patients such that polypharmacy is often practiced. Both aging and kidney disease can modify drug-drug interactions, including a) the affinity of some drugs for their specific receptor, b) the number of receptors present, and c) the cellular response upon activation of the receptor by the drug/s[3].

Elderly patients with kidney disease are more susceptible to the risks of adverse drug-drug interactions. Because this risk increases with the number of drugs concomitantly used, the number of medications prescribed should be the lowest possible, carefully balancing their risks and benefits in such patients. The consequences of polypharmacy include poor patient compliance due to high pill burden, increased cost of care, most importantly, drug-drug interactions (DDIs), which may have deleterious effects. Not all patients taking interacting drugs experience adverse consequences, but it is advisable to take due precautions to avoid mishaps in all cases where interactions are possible. Hence, this study was undertaken to evaluate drug interactions and to translate the findings into clinically observable benefits for patients.

Objectives:

To identify the DDIs among the drugs prescribed to CKD patients with or without other comorbidities.

Materials and methods: A Cross-sectional study was conducted in the Department of Nephrology, King George Hospital, Visakhapatnam from 1st August 2019 to 1st August 2020. A total of 80 patients with Chronic Kidney disease patients from the Nephrology department who fulfilled the selection criteria were included in the study. The sample size was calculated using the formula 4PQ/L2 with absolute precision of 10% with reported prevalence of CKD from <1% to 13%[4]. Patients with chronic kidney disease with other comorbid conditions, CKD patients of either sex above the age group of 18 years were included in this study.

The following data was collected using case proforma.

a. Demographic data: Patient Name, Age, Sex & Address
b. Disease data: CKD stage, comorbidities
c. Drug data: Drugs prescribed, dosage, duration, frequency, route of administration
d. DDI identification: LEXICOMP drug interaction software (Wolters Kluwer Analytics) that provides an internationally known pharmacopeia.

The data from the proforma was fed into Microsoft Excel to create a database file.

Statistical Analysis: Data entry and statistical analysis were performed using Microsoft excel 365 andSPSSv.24 (SPSS Inc., Chicago, IL, USA). The demographic variables were represented using percentages/ proportions (continuous variable represented using mean + SD & frequencies), and percentages were calculated for categorical variables. Prevalence of DDI was described using proportion or percentage.

Results

Table 1: Age distribution of study population

Age group	No. of patients	Percent (%)
18-30 years	14	17.5
31-50 years	32	40.0
51-70 years	32	40.0
≥ 71 years	2	2.5
Total	80	100.0

Figure1: Gender distribution of the study population

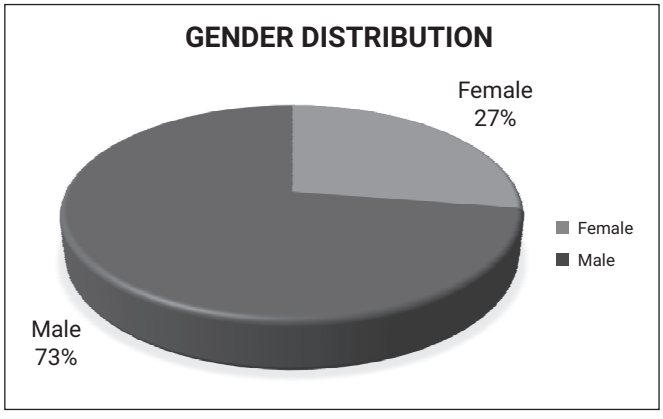

Table 2: CKD stage distribution among the patients

CKD Stage	No. of patients	Percent (%)
Stage 3	11	13.8
Stage 4	14	17.5
Stage 5	55	68.8
Total	80	100.0

Comorbidities: Among the 80 patients, Hypertension is the most predominant comorbidity found in our study in 78 of them (97.5%), followed by anaemia with 66.3% (53), Type 2 Diabetes Mellitus 43.8 % (35). Other comorbidities were Heart conditions like Coronary artery disease, Ischaemic heart disease, and Dilated cardiomyopathy among nine patients (11.3%).

Respiratory diseases like Pneumonia (5%), Pulmonary Hypertension with pulmonary edema (5%), Bronchial Asthma (3.8%), Bronchitis (2.5%), URTI (1.25%), and TB (1.25%) were found.

Other kidney disorders that are commonly associated with CKD, like IgA Nephropathy (5%), Polycystic Kidney (1.25%), Uremia (1.25%), and hyperkalemia (1.25%), were also found.

Viral hepatitis infections like Hepatitis C (3.8%) and Hepatitis B (1.25%) were found in three and one patients. CNS conditions like Seizures (2.5%), Cerebrovascular accidents (1.25%), and depression (1.25%) were also found.

Other comorbid conditions like Hypothyroidism (5%), Cholecystitis (1.25%), duodenal ulcer (1.25%), and peripheral vascular disease (1.25%) were also observed in three separate patients.

Drugs prescribed:

Table 3: Number of medications per prescription for the patients

No. of drugs per prescription	No. of patients	Percent (%)
Five or Less	16	20
6 - 10	53	66.3
11 - 15	10	12.5
16 or More	1	1.2
Total	80	100.0

A total of 604 drugs were prescribed for the 80 patients in our study, with a mean of 7.55 ± 2.73. The most common medications prescribed in order of frequency were Amlodipine n=38 (6.3%), Calcium preparations n=36 (6%), Pantoprazole n=36 6%), Clonidine n=32 (5.3%), Prazosin n=24 (4%), Aspirin n=23 (3.8%), Furosemide n=20 (3.3%), Metoprolol n=19 (3.1%), Nifedipine n=16 (2.6%), Atorvastatin n=15 (2.5%), Ranitidine n=15 (2.5%), clopidogrel n=14 (2.3%) and so on. Most of the patients were also prescribed Erythropoietin, vitamin supplements.

Prevalence of Drug-drug Interactions:

Out of 80 CKD patients included in the study, potential drug-drug interactions (pDDIs) were identified in 74 patients (92.5%). Forty - six of 74 (62.2%) showed 1 to 5 pDDIs, 22 patients showed 6 to 10 pDDIs, four patients showed 11 - 15 pDDIs, and two patients showed 16 to 20 pDDIs.

Figure 2: Pie diagram showing gender distribution of potential DDIs among the patients.

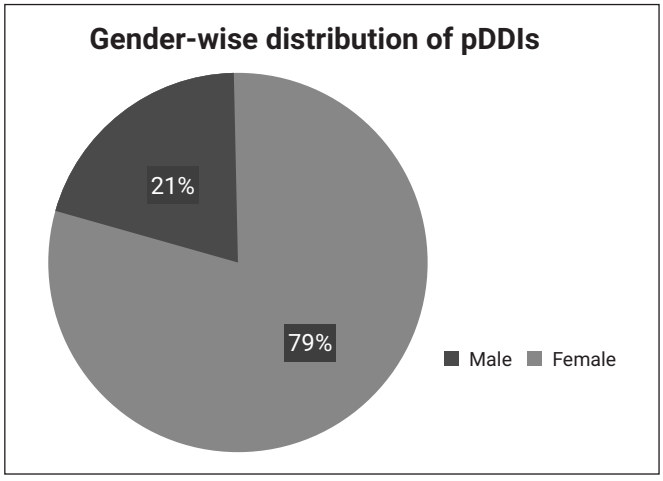

Table 4: Number of potential Drug-drug interactions among different age groupsofpatients

Age group	No. of potential DDIs	Percent (%)
18-30 years	49	12.7
31-50 years	167	43.1
51-70 years	155	40.1
≥ 71 years	16	4.1
Total	387	100.0

Lexicomp® severity classification: According to the Lexicomp® severity classification, 2 (0.5%) pDDIs were Type A (no known interaction), 55 (14.3%) were Type B (mild severity), 270 (69.8%) were Type C (moderate severity), 57 (14.7%) were Type D (major severity), and 3 (0.7%) were Type X (avoid drug combination).

Table 5: Most common potential drug-drug interactions (pDDIs) among variousseverity classes according to LEXICOMP®

Severity of pDDIs	Number	pDDIs	Frequency/ Percent (%)
Type B (mild severity)	55	Ranitidine - Calcium carbonate	10 (2.6%)
		Aspirin - Calcium carbonate	8 (2.1%)
		Ranitidine - Sodium Bicarbonate	6 (1.6%)
Type C (moderate severity)	270	Amlodipine - Calcium carbonate	14 (3.6%)
		Amlodipine - Prazosin	12 (3.1%)
		Calcium carbonate - Nifedipine	12 (3.1%)
Type D (major severity)	57	Metoprolol - Clonidine	11 (2.8%)
		Iron - Calcium carbonate	10 (2.6%)
		Iron - Sodium Bicarbonate	6 (1.6%)

Type A interactions do not have any pharmacodynamic effects.

Table 6: Effects of various potential drug-drug interactions (pDDIs)

Potential DDIs	Effect of pDDIs	Class	Frequency/ Percent (%)
Amlodipine - Calcium carbonate	Calcium salts diminish the therapeutic effect of Calcium channel blockers	Type C (Moderate Severity)	14 (3.6%)
Amlodipine - Prazosin	Prazosin may enhance the hypotensive effect of Calcium channel blockers	Type C (Moderate Severity)	12 (3.1%)
Calcium carbonate - Nifedipine	Calcium salts diminish the therapeutic effect of Calcium channel blockers	Type C (Moderate Severity)	12 (3.1%)
Metoprolol - Clonidine	Clonidine may enhance the AV blocking effect of Metoprolol and may also cause sinus dysfunction	Type D (Major Severity)	11 (2.8%)
Iron - Calcium carbonate	Calcium salts reduce Iron absorption	Type D (Major Severity)	10 (2.6%)
Ranitidine - Calcium carbonate	Calcium salts decrease the serum concentration of H2 receptor antagonists	Type B (Minor Severity)	10 (2.6%)
Aspirin - Calcium carbonate	Calcium salts decrease the serum concentration of Salicylates	Type B (Minor Severity)	8 (2.1%)
Prazosin - Metoprolol	Metoprolol enhances the hypotensive effect of Prazosin.	Type C (Moderate Severity)	8 (2.1%)
Ranitidine - Sodium Bicarbonate	Sodium bicarbonate decreases the serum concentration of H2 receptor antagonists	Type B (Minor Severity)	6 (1.6%)
Iron - Sodium Bicarbonate	Sodium bicarbonate decreases Iron absorption	Type D (Major Severity)	6 (1.6%)
Chlorpheniramine - Ipratropium Bromide	Ipratropium Bromide enhances the anticholinergic effects of Cetirizine	Type X (Avoid combination)	2 (0.5%)
Glyceryl Trinitrate - Sildenafil	Sildenafil (PDE5 inhibitor) enhances the hypotensive effect of Vasodilators like Glyceryl Trinitrate	Type D (Major Severity)	1 (0.3%)

Discussion: Approximately 37 to 60% of all patients above a certain age admitted to the hospital may have one or more potential drug interactions among the drugs they take at the time of admission. After admission, they are inadvertently added on with new medicines in their course of treatment, increasing the chances of occurrence of potential DDIs.[5]DDIs are becoming a significant concern for patients and health care personnel, as polypharmacy is evidently more common and essential in managing complex chronic diseases with other comorbidities, and the consequences from these may range from minor interactions like reduced uptake of the drug to altered excretion leading to severe toxic effects due to increased blood levels[6]. Polypharmacy and Over the counter (OTC) usage of drugs is quite common in India, especially in the elderly and individuals with chronic diseases with multiple comorbidities,

leading to increased interactions among the various medications they take.

In this cross-sectional study involving 80 CKD patients, the study group's age range was 22-77. The mean age of the patients in our study group was 47.2375 ± 14.37. In this study, most patients lie in the age group of 31 - 70 years (64, 80%). The study conducted by Al-Ramahi et al. shows that the mean age of the study population was 50.67 ± 15.93, and the most common age group of CKD patients are in between 30 - 60 years, 151 (54.9%) out of 275 total study subjects which is very much similar to this study[7]. Another study conducted by Chacko SC et al. shows that the study population's mean age was 56.14 ± 13.49, where most of the study subjects belong to the age group of 50 to 70 years[8]. In contrast, a study conducted by Santos-Díaz G et al. showed that the mean age of the study population is 77.1 ± 10.4, and most of the CKD patients are in the age group of above 80 years, 49 (43.7%) out of 112 CKD patients[6].

In this study, out of 80 patients, 58(72.5%) were males, and 22(27.5%) were females. This study shows male preponderance similar to the study conducted by Chacko SC et al., where 87 (77.1%) were males, and 63 (23.1%) were females out of 150 subjects[8]. Another study conducted by Rama M et al. also showed a male preponderance of 74.15% out of 205 subjects.[10] In contrast study conducted by Santos-Díaz G et al. showed a female majority of 61.6% out of 112 patients[9].

In this study, according to the staging of CKD, out of 80 patients, 55 (66.8%) subjects were in stage 5 of disease, followed by 14 (17.5%) subjects in stage 4 and 11 (13.8%) in stage 3, which shows that most of the study subjects belong to stage 5 category. It is similar to the study conducted by Rama M et al., which shows that most of the patients are in the stage 5 category (68.48%)[10]. Another study conducted by Chacko SC et al. also showed that most of the patients were in the stage 5 category, 79(90.8%)[8]. In contrast study conducted by Santos-Díaz G et al. shows that most of the study subjects were in the stage 3 category, 67 (59.8%)[9].

In this study, the most predominant comorbidity associated is Hypertension (97.5%) which is similar to the study conducted by Chacko SC et al. where the most common comorbidity associated with CKD is Hypertension (36.7%), Diabetes Mellitus (32.7%), Ischaemic Heart disease (10.73%)[8]. Another study conducted by Santos-Díaz G et al. also shows that the most common comorbidity associated with CKD is Hypertension (46.4%), Dyslipidaemia (29.5%), Diabetes Mellitus (22.3%)[9].

In this study, CKD patients have been prescribed a minimum of 2 drugs to a maximum of 16 drugs. A total of 604 drugs were prescribed for the 80 patients, with a mean number of prescribed medications per patient was 7.55 ± 2.73. Most of the patients (53, 66.3%) were receiving around 6 to 10 drugs per prescription, which is similar to the study conducted by Santos-Díaz G et al.[9] where 59 patients out of 112 subjects were receiving about 6 to 10 drugs per prescription. Another study conducted by Olumuyiwa JF et al. shows that 51 patients out of 123 subjects were receiving 11 to 15 drugs per prescription, followed by 43 patients were receiving 6 to 10 drugs per prescription[6]. Patients receiving three or more medications are at substantial risk of polypharmacy associated adverse DDIs, and the occurrence of DDIs are high among patient with progressed CKD stage.

In this study, most frequently prescribed drug in this study was Amlodipine 38 (6.3%). In contrast, Santos-Díaz G et al. study shows that the most used drugs were hydrochlorothiazide (15%), acetylsalicylic acid (10%), and furosemide (9%)[9]. Another study conducted by Adanne OE et al. shows that the most frequently prescribed drugs were furosemide (11.7%), lisinopril (9%), and Amlodipine (7.4%)[12].

In this study, out of 80 patients, 74 patients showed potential drug-drug interactions. A total of 387 interactions were identified. The most common interactions 270 (69.8%) encountered in this study were of moderate severity (Type C) followed by Type D major severity interactions 57 (14.7%), which was similar to the study conducted by Santos-Díaz G et al. where most of the interactions of 717 (77.3%) were Type C (moderate severity), 106 (11.4%) were Type D (major severity)[9].

In this study, the most frequent drug combinations with potential DDIs were Amlodipine + Calcium carbonate 14, Amlodipine + Prazosin 12, Metoprolol + Clonidine 11 and these drugs are responsible for causing Moderate and Major DDIs. Al-Ramahi et al. study findings show that the most common potential DDI was CaCO3 + Amlodipine, followed by aspirin + CaCO3, which is similar to this study[7]. In contrast, Rama M et al. found that the most common potential DDI were ascorbic acid + cyanocobalamin[3, 6]. Another study by Sgnaolin et al. also has a contrast result to the present study where the most common potential DDI were Atenolol + CaCO3 followed by Iron + CaCO3[13].

The patients in this study were prescribed with antidiabetic, antihypertensive, cardiovascular drugs, various nutritional and other supportive medicines, so several potential DDI outcomes were seen.

Table 7: Comparison of demographic data, clinical data, and severity of potential DDIs with other studies

Study	No. of Patients	Years (Mean ± SD)	Country	CKD stage - 5	DI software used	No. of drugs per patient (Mean ± SD)	Most common drug combination with pDDIs (%)	No of contra-indications
Rama M et al.[10]	205	48.6 ± 16.2	India	68.5%	Micromedex	12.1 ± 6.3	Ascorbic acid + Cyanocobalamin (12.4%) Clonidine + Metoprolol (3.8%)	0 (0.0%)
Sgnaolin et al.[13]	65	59.1 ± 14.7	Brazil	100%	Micromedex	6.3 ± 3.1	Calcium carbonate + Atenolol (8.0%) Calcium carbonate + Ferrous Sulphate (8.0%)	2 (3.1%)
Chacko SC et al.[8]	150	56.14 ± 13.49	India	90.8 %	Micromedex	7.93	Aspirin + Clopidogrel (12.25%) Aspirin + Torsemide (9.3%)	0 (0.0%)
Al-Ramahi et al[7]	275	50.7 ± 15.9	Palestina	100%	LexiComp	7.9 ± 2.4	Calcium carbonate + Amlodipine (12.3%) Calcium carbonate + Aspirin (8.2%)	2 (0.7%)
Santos-Díaz G et al.[9]	111	77.1 ± 10.4	Spain	4.5%	LexiComp	8.6 ± 3.4	Acenocoumarol + Omeprazole (1.1%) Ferrous Sulphate + Omeprazole (1.0%)	10 (9.0%)
Present study	80	47.24 ± 14.37	India	68.8%	LexiComp	7.55 ± 2.73	Calcium carbonate + Amlodipine (3.6%) Prazosin + Amlodipine (3.1%)	3 (0.7%)

Conclusion:

The high prevalence of potential DDI in CKD patients demonstrated here reinforces the importance of medication use. The recognition of potential DDI and key combinations of drugs avoids treatment failure situations or minimizes drug toxicity. The risk factors associated with DDI and each drug added to a regimen significantly increases the risk of DDI. With proper vigilance and awareness of DDIs in patients with chronic disease with comorbidities, their occurrence can be limited to a minor significance. Hence, prior review of these prescriptions using drug interaction checkers like Lexicomp, Micromedex, or Medscape Drug interaction checker is essential before writing prescriptions.

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Conflict of interest: Nil
Source of funding: Nil

Date received: Aug 11th 2021
Date accepted: Oct 26th 2021