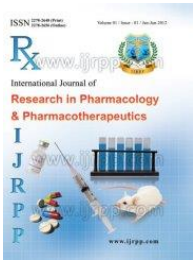
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.9 | Issue 1 | Jan - Mar - 2020***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Research article ***Open Access***

A study of drug-drug interactions in patients of chronic kidney disease at a tertiary care hospital

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ABSTRACT

Background

Chronic kidney disease (CKD) is one of the widely prevalent non-communicable diseases that is responsible for increasing morbidity in India. Drug therapy of CKD is complex and inevitably requires poly-pharmacy with frequent monitoring of drugs and their dosage adjustments.

Objectives

The main objective of the study was to identify the potential Drug-Drug Interactions (DDIs) among Chronic Kidney Disease (CKD) patients and to assess the risk factors possibly associated with these interactions.

Material and methods

After Institutional Ethics Committee approval, a prospective Cross-sectional study was carried out for a period of six months from 1st June 2017 to 30th November 2017 at department of Nephrology, of a tertiary care hospital. Patients diagnosed with CKD by treating Nephrologist were included and their prescriptions analysed. The prescriptions were then analysed for potential DDIs using MEDSCAPE multidrug interaction checker tool.

Results

Among 120 prescriptions, 79 patients had at least one interacting drug combination. Total number of potential DDI were 235. Majority of interactions were pharmacodynamic (50.21%) in nature. Severity assessment showed that majority of DDIs were moderate (64.68%) followed by minor (29.78%). Out of total prescribed drugs (618), DDIs were most commonly seen with cardiovascular class of drugs (46.8%). Considering individual drugs, five most commonly involved drugs in potential DDIs were calcium salts, aspirin, clonidine, furosemide and prazosin. Calcium carbonate +amlodipine were common drug combinations involved in potential DDI. Elderly age group, co-morbid conditions and increased number of drugs were the risk factors associated with the potential DDI.

Conclusions

This study highlights the need for proper therapeutic planning, routine monitoring of CKD patients, screening of prescriptions for potential DDIs to prevent possible DDIs.

Keywords: Drug-Drug Interaction (DDI), Chronic Kidney Disease (CKD), Polypharmacy.

INTRODUCTION

Chronic kidney disease (CKD) is characterized by multiple disorders affecting the morphology and functioning of kidneys. [1] It is a widely prevalent non-communicable disease that is responsible for increasing morbidity in India. [2] According to the World Health Organization (WHO), CKD contributes to nearly 850,000 deaths per year worldwide. [3]

Currently in CKD patients, the standard practice is to adjust the dose of renally eliminated medications so as to prevent adverse drug reactions as kidney functions decline in them. CKD not just impacts renal clearance mechanisms but also, nonrenal clearance mechanisms such as hepatic and intestinal cytochrome P450 (CYP) enzymes and drug transport proteins. Thus, making CKD patients more prone to develop drug toxicities, drug interactions etc. [4]

CKD patients often require multiple medications for management of their disease condition. Because people who have diabetes and hypertension are at high risk for developing CKD, and many CKD patients suffer from all three of these conditions together. They may also have other diseases or disorders (such as heart disease and high cholesterol), which will make it necessary for them to take medications for these conditions as well. Therefore, making pharmacotherapy of CKD complex and inevitably requiring poly-pharmacy with need for frequent monitoring of drugs and their dosage adjustments. Further, treatment of concurrent diseases adds to the complexity.

Due to disease itself and also due to the complex pharmacotherapy, patients of CKD, face several drug related problems like drug interactions, medication dosing errors, high incidence of adverse drug events which result in an increase in morbidity and mortality, as well as an increase in the overall cost of health care. Such patients are therefore, non-compliant to the treatment which is a hindrance to successful treatment outcome. Insight into the prescribing trends can help to identify, evaluate and minimize prescription errors and thereby decrease the burden of the disease. [5]

Drug-Drug Interactions (DDI) is said to occur when the effect of one drug is altered by the concurrent administration of another drug. It can occur either pharmacokinetically or pharmacodynamically. There is occurrence of pharmacokinetic interactions when either of the concurrently administered drugs have potential to alter other drug's pattern of absorption, distribution, metabolism and excretion. Similarly, there will be occurrence of pharmacodynamic interactions if concurrently administered drugs have similar or opposite effects.

The mechanism of an interaction can be important in predicting the time course of an interaction, and provides a way to minimize the risk of an adverse outcome. [6] Even though, DDIs are considered as preventable medication related problems, studies have found that up to 11% of patients experience symptoms associated with DDI and these are responsible for nearly 2.8% of hospital admissions. Monitoring of potential DDIs may improve the quality of prescribing and dispensing and it might form a basis for education focused on appropriate prescribing. [7]

Drug interactions (DIs) are common in clinical practice and are directly related to a number of factors such as polypharmacy, aging, hepatic metabolism, decreased renal function etc. Individuals with CKD due to requirement of multiple classes of drugs are at a greater risk for the development of DDIs. [8]

Hence this study was undertaken to analyse, drug-drug interactions in treatment of CKD patients. So that an awareness about the importance of drug monitoring and review in CKD patients is created. The main objective of our study was to identify the potential DDIs among CKD patient's and assess the possible risk factors associated with these interactions.

MATERIALS AND METHODS

Study design

A prospective, cross sectional, observational study was carried out at the Nephrology OPD of

Krishna Rajendra Hospital, Mysore for a period of 6 months from 1st June 2017 to 30th November 2017. Sample size was calculated to be 120 using estimation technique.

Inclusion criteria

Patients aged 18 years or more, of either sex, diagnosed by the clinician to have chronic kidney disease and currently on drug treatment were included in the study.

Exclusion criteria

Surgical conditions like kidney stone, tumors and trauma, Pregnant and lactating women, patients not willing to participate were excluded.

METHODOLOGY

After obtaining clearance from the Institutional Ethics Committee, subjects attending Nephrology department at Krishna Rajendra Hospital, attached to Mysore Medical College and Research Institute, Mysore, diagnosed with CKD by the treating Nephrologist, were included in the study after obtaining a written informed consent. The socio-demographic data along with other relevant details of the study subjects were collected from patient's OPD card and their prescriptions were analysed.

All the prescriptions of the study population were screened for DDIs by using computerized DDI database system (MEDSCAPE database). Certain demographic characteristics were studied to find out the predictors of DDIs, such as patient characteristics [gender, age (more than 18 years old), concurrent morbidities and length of stay], drug characteristic (number of drugs) were studied.

All the information collected was tabulated for analysis. The DDIs were also categorised according to different parameters such as severity (mild, moderate, severe), type of DDI (pharmacokinetic, pharmacodynamic, unspecified). [9]

STATISTICAL ANALYSIS

Data collected regarding the sociodemographic & DDIs were subjected to statistical analysis. Statistical Package for Social Sciences (SPSS) software version 20 was used for the descriptive analysis.

Descriptive statistics like mean and median was used for continuous variables and frequency and percentage for categorical variables.

Probability (p) value of less than 0.05 was considered to be statistically significant for all analysis.

RESULTS

In the current study prescription of 120 CKD patients was analyzed during the study period of 6 months.

Demographics

Out of 120 patients studied, 98 (81.7%) were male and 22(18.3%) were female patients (Table-1 & Figure-1). In our study there was a male preponderance over the female patients.

Table 1: Gender distribution

Sex	No. of patients	Percentage (%)
Male	98	81.7
Female	22	18.3

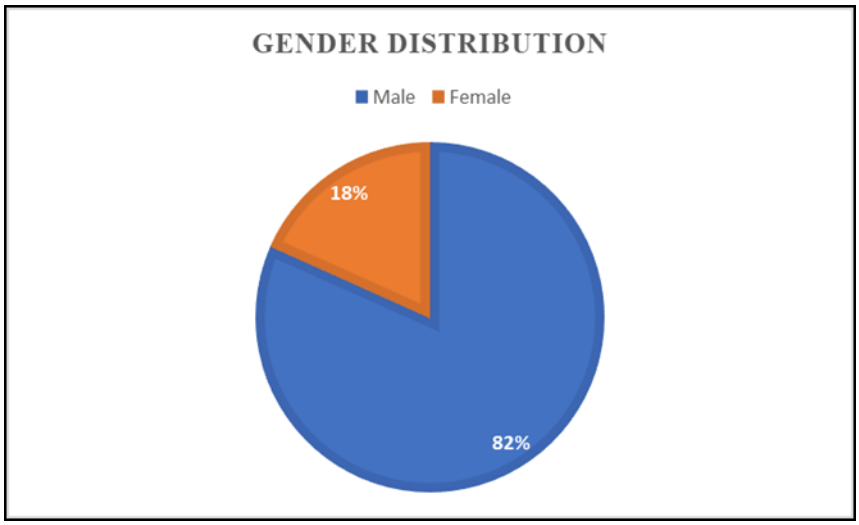

Figure-1- Gender distribution of CKD patients

Age distribution

Majority of patients were in the age group of 41-50 years (41.7%), with a mean age of 47.56 years (Table-2 & Figure-2) and majority of patients were belonging to stage 4 and more of CKD.

Table 2: Age distribution

Age (years)	No. of patients	Percentage (%)
18- 20	2	1.7
21- 30	8	6.7
31- 40	23	19.2
41- 50	50	41.7
51- 60	19	15.8
>61	18	15.0

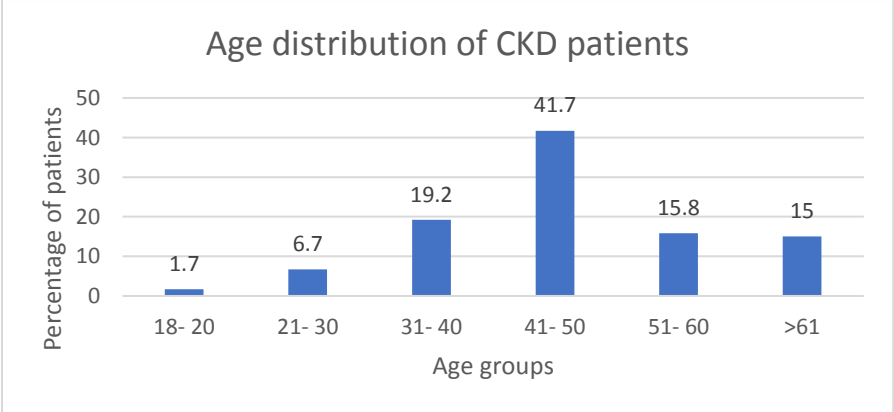

Figure-2: Age distribution of CKD patients

Co-morbidities

Most frequently encountered co-morbidity in CKD patients was hypertension (40%); followed by combination of hypertension and diabetes (7.5%), diabetes (4.2%), anaemia (4.2%) and a combination of ischaemic heart disease (IHD) and hypertension (4.2%). (Table-3 & Figure-3)

Table 3: Co-morbidity assessment

Co-morbidity	No. of patients	Percentage (%)
Hypertension	48	40.0
Hypertension and diabetes	9	7.5
Diabetes	5	4.2
Anaemia	5	4.2
IHD + hypertension	5	4.2
Hypothyroid	2	1.7

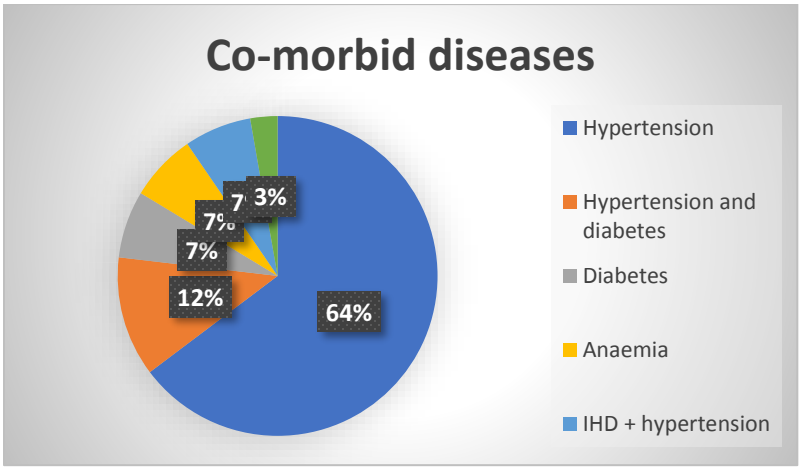

Figure-3: Co-morbid diseases seen in CKD patients

Drug-drug interactions

In our current study, 120 prescriptions were analysed. Total number of drugs prescribed was 616. Average number of drugs per prescription was 5.13. Total number of DDIs seen was 235. Out of 120 prescriptions, 79 had at least one potential interacting combination. Average number of interactions per prescription was 1.96.

Among the DDIs seen, pharmacodynamic interactions (50.21%) were the commonest ones, followed by pharmacokinetic (37.45%) and unspecified interactions (12.34%). (Table 4 & Figure-4).

Of all the DDIs seen 64.68% were moderate, 29.78% were mild and only 4.68% were serious in nature. (Table 5 & Figure-5).

Aspirin was a common interacting drug with other drugs, followed by calcium carbonate, clonidine, frusemide and metoprolol. (Table 6 & Figure-6)

Calcium carbonate and amlodipine were the commonly involved drug combination in DDIs in CKD patients. Other interacting combinations include Calcium acetate + amlodipine, Calcium acetate + ferrous sulphate, Ranitidine + ferrous sulphate and Aspirin + clopidogrel. (Table 7 & Figure-7).

Most commonly involved class of drug according to ATC system of classification of drugs were Cardiovascular, followed by blood and blood forming drugs and alimentary group.

Table 4: Type of drug interactions.

Type of drug interaction	Percentage
Pharmacokinetic	37.44%
Pharmacodynamic	50.21%
Unspecified	12.34%

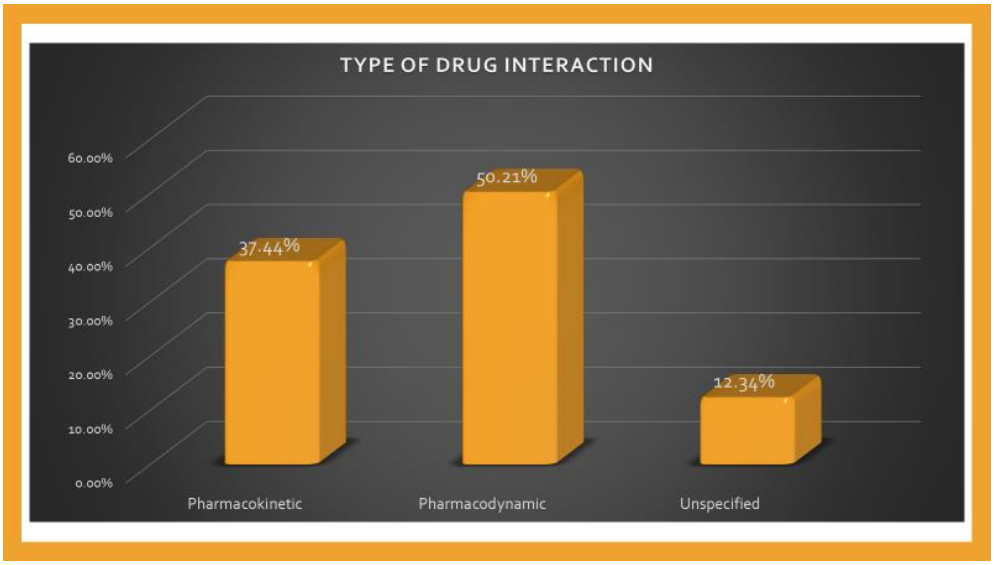

Figure-4: Types of drug interaction

Table 5: Severity of drug interaction

Severity of drug interaction	Percentage (%)
Serious	4.68
Moderate	64.68
Mild	29.78

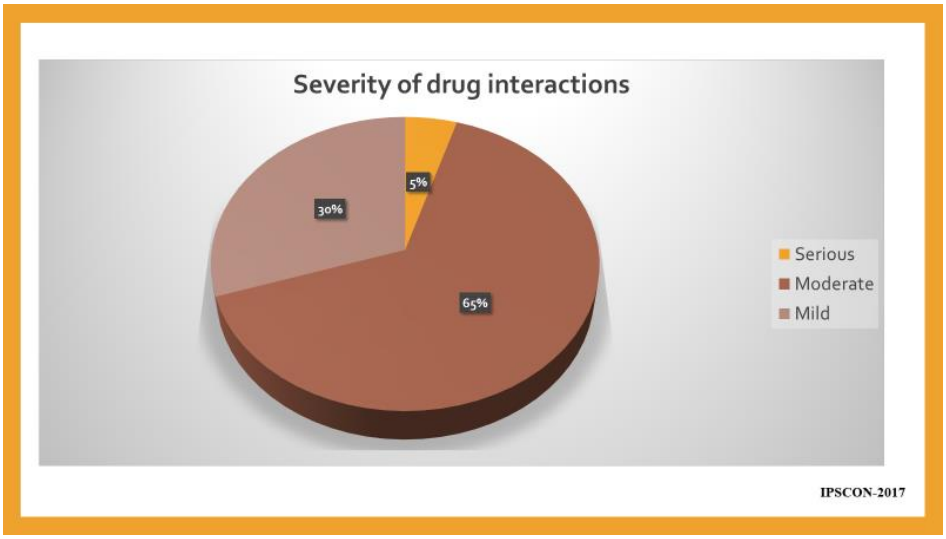

Figure-5: Severity of drug interactions

Table 6: Commonly prescribed drugs involved in DDIs in CKD patients

Sl.no	Commonly prescribed drugs	
1	Aspirin	23
2	Calcium acetate	26
3	Clonidine	21
4	Prazosin	18
5	Ferrous sulphate	11
6	Calcium carbonate	29
7	Furosemide	19
8	Metoprolol	18

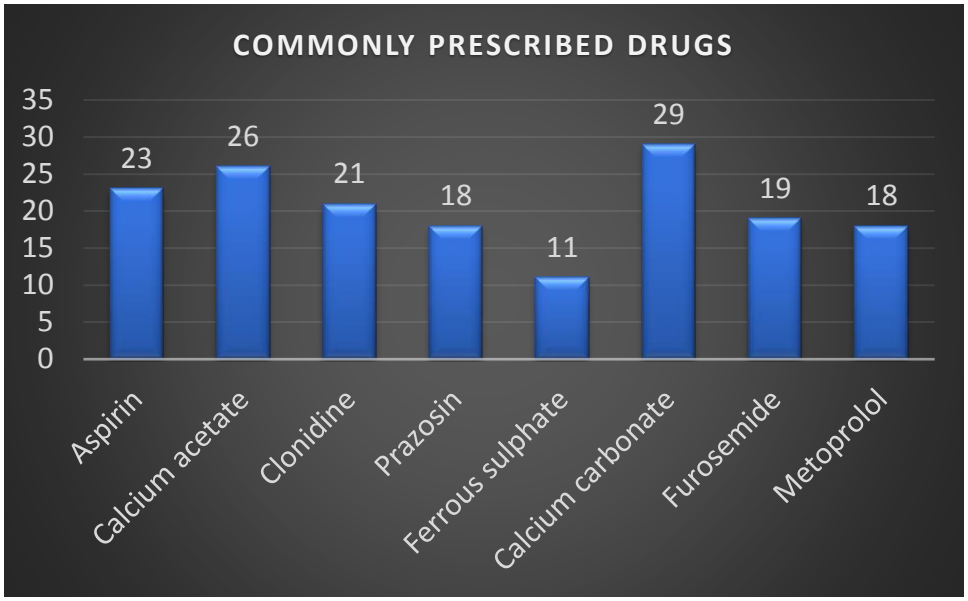

Figure-6: Commonly prescribed drugs involved in DDIs in CKD patients

Table 7: Commonly involved combinations of drugs involved in DDIs in CKD patients

Sl.no	Commonly involved combinations	Number of interactions	Type of drug interaction	Potential consequences
1	Clopidogrel + torsemide	2	Pharmacokinetic	Increased levels of torsemide
2	Calcium acetate + amlodipine	9	Pharmacodynamic	Decreased amlodipine effect
3	Aspirin + clopidogrel	4	Pharmacodynamic	Bleeding
4	Pantop + ferrous sulphate	2	Pharmacokinetic	Decreased FeSO4 effect
5	Rantac + ferrous sulphate	6	Pharmacokinetic	Decreased FeSO4 effect
6	Calcium carbonate + amlodipine	15	Pharmacodynamic	Decreased amlodipine effect
7	Calcium acetate + ferrous sulphate	9	Pharmacokinetic	Decreased FeSO4 effect
8	Clonidine + metoprolol	1	Pharmacodynamic	Either increases toxicity of other

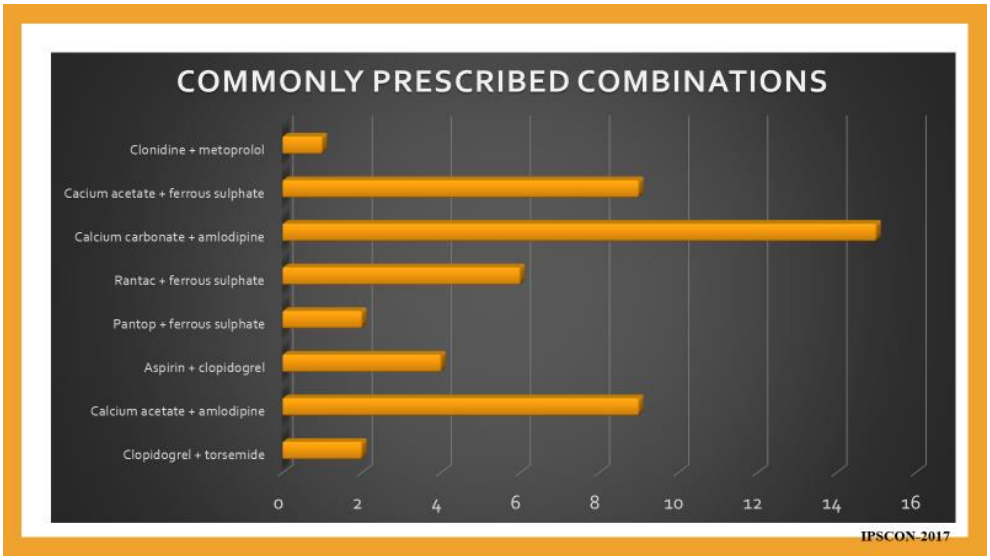

Figure-7: Commonly prescribed drug combinations involved in DDIs in CKD patients

DISCUSSION

Chronic kidney disease (CKD) is a major public health issue because of rising incidence, poor outcome and expensive treatment, thereby imposing a burden on social and health care systems. [10] Our current study highlights the detection of DDI prevalence using computerized DDI database system, to check prescriptions of CKD patients attending nephrology OPD of a tertiary care hospital. Where patient's data of various drug intake was analysed using the software and various drug interactions were studied to determine the severity of these interactions and their significance as far as CKD pharmacotherapy was concerned.

In our current study the mean age of patients was found to be 47.56 years and majority of patients were in the age group of 41-50 years. This was similar to the findings observed in the study conducted by Rama et al [6] and Al-Ramahi et al. [11] In India incidence of diabetes is highest in the age group of 45-60 years. [12] Even the incidence of hypertension increases after 45 years of age. [13] Diabetes and hypertension being important comorbidities, seen to be associated with CKD, might be one of the reasons of majority of CKD patients falling in the 41-50 age group in our study.

There was a male preponderance over the female patients. Out of 120 patients studied, 98 (81.7%) were male and 22(18.3%) were female patients. This finding is in concurrence with study done by Al Ramahi et al. [11] CKD progression differs depending on the gender. Studies have shown that male patients show a substantially higher prevalence of CKD and incidence rate of ESRD than those observed in female patients. There are also studies which suggest that, men with diabetes have a higher risk of nephropathy than women with diabetes do. [14] This might be one of the reasons for male preponderance in our study.

Majority of patients belonged to stage 4 and more of CKD, this was also consistent with the study conducted by Ahlawat et al. [2]

Diabetes and hypertension are the leading aetiologies of CKD worldwide. In our present study hypertension (40% of cases) was the commonest co-morbidity; followed by combination of hypertension and diabetes, diabetes, anaemia and a combination of ischaemic heart disease (IHD) and hypertension. These findings were similar to Ahlawat et al. [2] where hypertension was found to be common co-morbidity (55%), followed by diabetes, and anemia. However, the incidence of hypertension as comorbidity with CKD was higher (84%) in studies conducted by Al Ramahi et al. [11]

Out of the total 120 prescriptions analysed during our study, 79 (65.8%) had at least one potential interacting combination. This was found to be lower than what was found in the studies conducted by Al Ramahi et al [11] and Fasipe et al [15] (89.1% and 95.9% respectively).

In our study average number of drugs per prescription was 5.13, which is smaller than the average number of drugs reported by Ahlawat et al

[2], and Rama et al [6] (6.57, and 12.08 respectively). This difference in the average number of drugs may be due to the study population size, co-morbid conditions and physician prescribing behaviour.

Average number of interactions per prescription was 1.96. this is higher than Fasipe et al [15] study (1.24). but lower than the figure reported by Rama et al.[6] and Marquito et al. [8] (2.7 in both the studies). This, therefore, highlights the need for physicians to regularly evaluate prescriptions for CKD patients for DDI.

Pharmacodynamic interactions were commonly seen, followed by pharmacokinetic and unspecified interactions (50.21%, 37.44% & 12.34% respectively). This was similar to reports of Rama et al[6] and Hegde et al, [16] stating that pharmacodynamic interactions are the commonest type of DDIs seen. But the study conducted by Fasipe et al [15] reported pharmacokinetic interactions as the commonest type of DDI.

According to their severity and undesirable effects the drug-drug interactions are classified as mild, moderate and severe. Mild drug-drug interactions limit clinical effects. These usually do not require a change in the therapy as they manifest either as an increase in the frequency or increase in the severity of the adverse effects. but Moderate drug-drug interactions may result in exacerbation of the disease of the patient and/or a change in the therapy. The severe drug-drug interactions are the ones which are life threatening and/or they require medical treatment or an intervention to minimize or to prevent the severe adverse effects. [17]

Most of the drug interactions in our study were moderate in nature (64.7%) followed by mild interactions (29.78%) and only 4.68% were severe in nature. Similar result was seen in a study conducted by Al Ramahi et al. [11] This confirms that not all cases of DDI require discontinuation of drugs.

Cardiovascular, followed by blood and blood forming drugs and alimentary group of drugs were commonly prescribed drugs according to ATC classification of drugs. Considering individual drugs, five most commonly involved drugs in potential DDIs were calcium salts (Calcium acetate and calcium carbonate), aspirin, clonidine, furosemide and prazosin. This was similar to previous studies which showed that calcium carbonate and furosemide were among the most frequently prescribed medications. [8, 11]

Aspirin had many pharmacokinetic and pharmacodynamic interactions and few of them were also serious interactions like interaction between aspirin and ramipril resulted in further decrease in renal functions.

Commonly involved combinations of drugs involved in DDIs in CKD patients were Calcium carbonate + amlodipine followed by Calcium acetate + amlodipine and Calcium acetate + ferrous sulphate. The most common potential DDI in studies conducted by Fasipe, et al [15], Hedge et al.[16] and Sgnaolin et al.[18] was between oral calcium carbonate and oral ferrous sulphate.

It is very important to evaluate the prescribing pattern in CKD patients on a time to time basis, so as to identify potential DDIs, try to prevent it, thereby improving patient condition and compliance to therapy. Identifying, categorising of DDIs is very essential to understand the adverse effects of drugs given to CKD patients.

To minimise DDIs from developing various strategies can be developed like, firstly trying to make therapy tailored to individual patient needs, taking into account patient's disease condition, co-morbidities associated with disease, affordability etc. As DDI chances are increased with prescription of multiple drugs which we commonly come across when CKD pharmacotherapy is considered. Secondly development of educational programs and improving patient's counselling to avoid improper use of medications. Thirdly patients should be asked to report any adverse effect that they experience to their treating physician, so that, their data can be used as a data base when treating other CKD patients, and thereby reducing the unwanted effects of drug combinations to a minimum. Fourth, physicians and pharmacologist should be well versed with the drug actions, its adverse effects and interactions, this can be done by learning from their clinical experience, literature reading about the drug, use of internet based DDI checker

To minimize the consequences of DDIs both clinicians as well as pharmacists can use the DDI database freely available online, learn from their clinical experience, literature reading about the drug etc. Apart from, proper therapeutic planning, there should also be a routine monitoring of serum electrolytes, blood glucose, coagulation profile, hepatic and renal functions in CKD patients. At the same time confirmation of pDDIs clinically as well

as by pharmacokinetic studies especially for significant and severe DDIs are essential.

It is also important to remember that not all DDIs are harmful or life threatening. Some of drug combinations can be beneficial to the patients such as using ACE inhibitors along with a diuretic like thiazide, has a better control on BP and is a beneficial interaction. On the other hand, using an ACE inhibitor and a potassium sparing diuretic like spironolactone will result in hyperkalaemia in the patients, which is an undesirable interaction. So, it is important to give attention for patient's medication list before considering various drug combinations as desirable or undesirable drug interaction.

Finally, it has to be said that it is impossible to remember or document all clinically significant drug interactions, but the focus of this article was to highlight the most important and common interaction that we came across during our study in CKD patients.

The limitation of our study was that, potential DDIs detected were theoretical and may not occur in clinical settings all the time. In addition, the Medscape Interaction checker used in this study did not take into consideration some of parameters related to drugs like the prescribed dose, frequency of administration, route of administration and duration of medication. However, our study has brought to light the magnitude of potential DDIs among CKD patients and the need to take steps to reduce the additional burden on CKD patients.

In our study cardiovascular system of drugs were the commonest group of drugs prescribed according to ATC system of drug classification. Common risk factors associated with the potential DDI were elderly age group, co-morbid conditions and increased number of drugs. Most of the drug interactions were moderate in nature. Aspirin had many pharmacokinetic and pharmacodynamic interactions and few of them were also serious interactions. Calcium carbonate + amlodipine followed by Calcium acetate + amlodipine and Calcium acetate + ferrous sulphate were the commonest interacting drug combinations.

Drug therapy in CKD requires prescription of multiple drugs due to associated co-morbid conditions. Drug interactions are an important cause of adverse effect. This study provides an overview of the importance of routine monitoring of CKD patients & screening their prescriptions for potential DDIs to prevent possible DDIs and to reduce the incidence of preventable DDIs significantly. So that the patient receives utmost health benefit from the drug therapy.

ACKNOWLEDGEMENTS

Authors would like to thank the Head of the departments and teaching staff of Pharmacology and Nephrology department for their co-operation.

Funding: No funding sources

Conflict of Interest: None declared

Ethical Approval: The study was approved by the Institutional Ethics Committee

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