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Original Research Article

Identification of Drug Related Problems among Chronic Kidney Disease Patients in A Tertiary Care Hospital

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Abstract

Medication therapy to Chronic Kidney Disease patients is complex because of the co morbidities and the major risk associated with these patients. A prospective, cross sectional study was conducted for a period of 6 months in a tertiary care hospital. A total of 130 patients, aged 18 years or older, diagnosed with all stages of Chronic Kidney Disease were included in the study. Patient data were collected from the patient medical records, the prescriptions were analyzed and the drug related problems were identified and classified according to Hepler and Strand. Descriptive analysis was done for age, gender, stages, drugs and Drug Related Problems. A total of 1454 drugs were prescribed for the patients with an average of 13.3±3.53 drugs per prescription. An average of 1.25±1.23 Drug Related Problems per prescription were observed among the study population. The most common Drug Related Problems identified was Adverse Drug Reactions (11.53%) and Drug combinations to use with caution and need close monitoring (11.53%), followed by over dose 9.23%. Other Drug Related Problems identified were untreated indication 7.69%, Drug without indication 3.08%, improper drug selection 1.53%, Treatment duplicity 0.76%, and potential Drug interactions 80.00%.Continual identification and resolution of Drug Related Problems in Chronic Kidney Disease could play a vital role in achieving better clinical outcomes.

Keywords: Drug Related Problems, Chronic Kidney Disease, Adverse Drug Reactions, polypharmacy, Co morbidities, Drug interactions.

INTRODUCTION

Chronic Kidney Disease (CKD) is defined as the presence of kidney damage or decreased Glomerular Filtration Rate (GFR) for 3 months or more [1]. Medication therapy to Chronic Kidney Disease patients is complex because of the comorbidities and the major risk associated with these patients. CKD is a global threat to health in general and for developing countries in particular, because therapy is expensive and lifelong [2]. It is highly prevalent and is increasing in public health concern as the number of people affected by it is increasing each year [3]. As CKD progresses, the drugs that are given for these patients also increases and the prevalence of drug related problems also increases [4].

A Drug Related Problem is an event occurring as a result of the drug therapy that actually or potentially interferes with desired health outcomes [5]. A thorough knowledge of DRPs may help in identifying DRPs, resolving actual DRPs and preventing potential DRPs for the provision of better patient care.

Categories of DRPs

According to Hepler and Strand classification, DRPs are broadly classified into eight categories [4].

Indication without drug (IWD) / Untreated Indication

Indication without drug means the patient is not receiving a drug for a given medical condition despite the need for such a drug [6].

Drug without Indication (DWI)

Drug without indication (DWI) means the patient has no valid medical indication for taking a certain drug [6].

Improper Drug Selection (IDS)

Improper drug selection (IDS) means the patient is taking the wrong drug for a given medical condition [6].

Sub Therapeutic Dosage (STD) / Under Dosage (UD)

Sub-therapeutic dosage (STD) means the patient is taking too little of the correct drug for a given medical condition [6].

Over Dosage (OD)

Over-dosage (OD) means patient is taking too much of the correct drug for a given medical condition [6].

Adverse Drug Reactions (ADRs)

Adverse drug reaction (ADR) means that unwanted/unpleasant or harmful drug effects caused a medical condition in a patient [6, 7].

Drug Interactions (DI)

DI can be defined as the set of alterations introduced up on the therapeutic effect of a given drug stemming from the co-administration of one or more medications [8, 9].

Failure to Receive Drug (FRD)

Failure to receive drug (FRD) means patient is not receiving prescribed medications for a given medical condition [6].

METHODOLOGY

This study was a Prospective cross sectional, observational study conducted for a period of 6 months with a total of 130 patients whose age greater than 18 years or older, diagnosed with all stages of Chronic Kidney Disease in a tertiary care hospital. Out patients, those having hepatic dysfunction, Pregnant and lactating women and critically ill patients were excluded from the study. The study was approved by Institutional Ethics Committee (IEC -VCMR) - EC/LTR/2018/010 of Vijaya Hospital. The data from the case sheets were taken in a data collection form specially designed for the study which includes the patient's demographics (age, sex, weight), co morbidities, past and present medications and medical history , fresh complaints, drug treatment regimens and lab reports (CBC, RFT, Blood Glucose levels, lipids and other tests).

CALCULATION OF GFR

Renal function i.e. GFR will be calculated using CKD – EPI calculators which involve the following equation

$$eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if Black]}$$

PRESCRIPTION ANALYSIS

The patient's case notes and drug chart were analyzed for the DRPs:

- Dosage Adjustments according to KDIGO Guidelines.
- Drug Interactions were assessed through MICROMEDEX Software.
- ADRs were assessed through Naranjo Algorithm were classified into definite (9-12), probable (5-8), possible (1-4), or doubtful (0).

DRP DOCUMENTATION

The identified DRPs were documented in DRP documentation form and necessary interventions were reported.

FOLLOW UP

Daily follow up until discharge were carried out.

STATISTICAL ANALYSIS

All the data collected were tabulated and analyzed statistically using STATA version 11.0 Descriptive analysis was done for age, gender, stages of CKD drugs prescribed and DRPs. Continuous variables was represented as Mean (SD) and categorical variables was represented as Frequency (percentage). Spearman's Correlation was performed to determine the occurrence of DRPs correlation with age, co morbidities and stages. The p value of <0.05 was considered as statistically significant.

RESULTS

A total of 130 patients were selected as per inclusion and exclusion criteria. Their demographic details were collected which is represented in the Table-1.

Table-1: Demography of the Study Population

Age in years Range	No. of Patients (n=130)	
	Frequency	Percentage
18-40	3	2.30%
41-60	57	43.84%
61-80	**62**	**47.69%**
>80	8	6.15%
Gender		
Male	85	65.38%
Female	45	34.61%
Comorbidities		
Hypertension	**118**	**37.10%**
Diabetes Mellitus	89	27.98%
Coronary Artery Disease	64	20.12%
Others	29	9.11%
Dialysis		
Yes	65	50.0%
No	65	50.0%

PREVALENCE OF CKD

The prevalence of Chronic Kidney Disease in the study population according to the stages of CKD as per National Kidney Disease Foundation classification was as follows: none of the patients were in CKD-I stage, 1(0.76%) were in CKD-II, 28(21.53%) were in CKD-III, 36(27.69%) were in CKD-IV, and 65(50.0%) were in CKD-V stage.

DRP-Drug Related Problems

Drugs prescribed in the study population is represented in Table-2. A total of 163 DRPs were identified which is indicated in Table-3. ADR and Contraindication were predominantly identified DRP.

Table-2: Drugs Prescribed In CKD Patients

Drugs	Category	Frequency	Percentage
Antihypertensives & Diuretics (n=310)	Calcium channel blockers	70	38.04%
	Centrally acting drugs	45	24.45%
	Beta blockers	35	19.02%
	Alpha blockers	20	10.86%
	Angiotensin receptor blockers	13	7.06%
	Angiotensin converting enzyme inhibitors	1	0.54%
	Furosemide/Torsemide	87	28.43%
	Spironolactone	18	5.88%
	Metalazone	11	3.59%
Anti-Diabetics (n=54)	Metformin	5	9.25%
	Newer drugs (Saxagliptin,Linagliptin,Vildagliptin)	4	7.4%
	Insulin	45	83.3%
Phosphate Binders and Iron Supplements (n=62)	Sevelamer	13	10.0%
	Erythropoetin	30	48.83%
	Folic acid	9	14.51%
	Ferrous fumarate + Folic acid	4	6.45%
	Ferrous sulphate + Folic acid	3	4.83%
Calcium and Vitamin D Supplements (n=46)	Calcium carbonate + Vitamin D3	18	39.13%
	Cholecalciferol	15	32.60%
	Calcitriol	12	26.08%
	Calcium citrate + Magnesium + Vitamin D3	1	2.17%
Antibiotics (n=175)	Cefoperazone+ Sulbactam	37	21.14%
	Piperacillin+Tazobactum	23	13.14%
	Meropenem	18	10.28%
	Ciprofloxacin	17	9.71%
	Clindamycin	15	8.57%
	Linezolid	14	8.0%
	Ceftriaxone	12	6.85%
	Metronidazole	10	5.71%
	Amikacin	7	4.0%
	Azithromycin	6	3.42%
	Vancomycin	6	3.42%
	Doxycycline	5	2.85%
Other Drugs (n=807)	Antianginal	129	13.9%
	PPI/H_2 Receptor Antagonist	127	13.75%
	Antiplatelet	99	10.72%
	Statins	75	8.1%
	Analgesics	52	5.63%
	Anticonvulsant	47	5.09%
	Sodium bicarbonate	45	4.87%
	Antiemetics	42	4.5%
	Thyroid drugs	30	3.25%
	Magnesium and Potassium Supplements	24	2.60%
	Anticoagulant	23	2.49%
	Febuxostat	23	2.49%
	Corticosteroids	12	1.30%
	Antifungal	12	1.30%
	Acetylcysteine	12	1.30%
	Dobutamine	10	1.08%
	Silodosin	8	0.86%
	Digoxin	5	0.54%
	Montelukast + Levocetrizine	5	0.54%

Table-3: DRPs Identified in the Study Population

Identified DRP	Frequency(n=130)	Percentage
Untreated indication	10	7.69%
Improper drug selection Drug choice problem	2	1.53%
Treatment duplicity	1	0.76%
Drug combinations to use with caution and need close monitoring	15	11.53%
Sub Therapeutic Dosage/ **Under Dose**	0	0
Failure To Receive Therapy	0	0
Over dose	**12**	**9.23%**
Adverse Reactions	**15**	**11.53%**
Potential Drug Interactions	**104**	**80.0%**
Drug Use without indication	4	3.08%

Potential drug interactions found in the study population is represented in Table-4.

Table-4: Potential Drug Interactions

Drugs	Interacting drugs	Mechanism	Effect	Frequency (n=104)	Percentage	Monitoring parameters
Digoxin	Nifedipine	Additive effects on AV node conduction	May result in digoxin toxicity; increased risk of complete heart block.	3	2.88%	Digoxin plasma concentration
	Metolazone	Diuretic-induced hypokalemia and hypomagnesemia enhance Na-K-atpase inhibition by cardiac glycosides		3	2.88%	Monitored for ECG signs of potassium depletion
	Spironolactone	Inhibition of active tubular secretion of digoxin		4	3.84%	Digoxin serum concentration
	Amiodarone	Inhibition of p-glycoprotein by amiodarone, and reduction of digoxin clearance		4	3.94%	Digoxin serum concentration
Tramadol	Ranitidine/ Ciprofloxacin	Inhibition of CYP3A4-mediated tramadol metabolism	Increased tramadol exposure and increased risk of respiratory depression.	2	1.92%	Closely monitor for seizures, serotonin syndrome
	Alprazolam	Additive CNS depression	Increased risk of respiratory and CNS depression	2	1.92%	Closely monitor for sedation and respiratory depression
	Fluconazole	Inhibition of CYP3A4-mediated tramadol metabolism	Increased tramadol exposure and increased risk of respiratory depression	2	1.92%	Monitor for signs of opioid withdrawal
Metronidazole	Ciprofloxacin/ Ondansetron / Fluconazole	Additive QT-interval prolongation	Increased risk of QT-interval prolongation and arrhythmias	7	6.73%	Require ECG monitoring
Fluconazole	Levofloxacin	Additive effects on QT interval	Increased risk of QT interval prolongation	8	7.69%	Require ECG monitoring
	Ranolazine	Inhibition of CYP3A-mediated ranolazine metabolism by fluconazole	Increased ranolazine plasma concentrations and increased risk for QT interval prolongation.	8	7.69%	Require ECG monitoring
Clopidogrel	Cilostazol /. escitalopram	Additive effects	Result in an increased risk of bleeding.	4	3.84%	Close monitoring for bleeding
Acenocoumarol	fluconazole	Decreased acenocoumarol metabolism	Increased risk of bleeding.	1	0.96%	Monitoring of the prothrombin time
Heparin	cefoperazone	Inhibition of platelet function, decreased	Increased risk of bleeding	2	1.96%	Monitoring of the prothrombin time

		synthesis of clotting factors				
Zolpidem	Alprazolam/ clonazepam	Additive effects	Increase in CNS depressant effects.	2	1.96%	Monitor for sedation
Clopidogrel	Amlodipine / Nifedipine	Inhibition of CYP3A4-mediated clopidogrel activation	Decreased antiplatelet effect and increased risk of thrombotic events.	5	4.80%	Monitored for loss of clopidogrel efficacy.
Clonidine	Metoprolol/ Nebivolol/ Bisoprolol	Unknown; unopposed alpha adrenergic stimulation	Increased risk of sinus bradycardia; exaggerated clonidine withdrawal response	13	12.5%	Monitored carefully for hypertension.
Nifedipine	voriconazole	Inhibition of CYP3A4-mediated Nifedipine metabolism	Increased risk of hypotension, bradycardia, or acute renal injury.	2	1.92%	Monitoring of heart rate and blood pressure
Fluconazole	Torsemide	Inhibition of CYP2C9-mediated torsemide metabolism by fluconazole	Increased torsemide exposure and increased risk of toxicity.	1	0.96%	Monitor patients for torsemide toxicity
Clopidogrel	Fluconazole	Inhibition of CYP2C19-mediated clopidogrel	Reduced platelet inhibition.	4	3.84%	Monitored for loss of clopidogrel efficacy
Heparin	Glyceryl trinitrate	Unknown	Decrease in partial thromboplastin time.	2	1.92%	Monitor PTT
Atorvastatin	Diltiazem	Inhibition by diltiazem of cytochrome P450 3A4-mediated atorvastatin metabolism	Increased risk of rhabdomyolysis.	4	3.84%	Monitor creatine kinase (CK) levels
Phenytoin	Quetiapine	Induction of CYP3A4-mediated quetiapine metabolism	Decreased quetiapine exposure.	2	1.92%	Monitor plasma concentration of phenytoin
Aspirin	Furosemide/ Spironolactone	Decreased renal prostaglandin synthesis	Reduced diuretic effectiveness and possible nephrotoxicity.	6	5.76%	Monitor for worsening renal function and serum potassium levels
Nifedipine	Phenytoin	Induction of CYP3A4-mediated Nifedipine metabolism	Decreased Nifedipine exposure.	2	1.92%	Monitor plasma concentration of phenytoin
Ramipril	Spironolactone	Increased potassium retention secondary to lowered aldosterone levels	Result in hyperkalemia	2	1.92%	Monitor potasium level
Diltiazem	Propranolol	Additive cardiovascular effects, decreased metabolism of beta blockers	Increased risk of hypotension, bradycardia, AV conduction disturbances.	1	0.96%	Monitor BP and HR
Aspirin	Metoprolol	Decreased production of renal prostaglandin	Increased blood pressure.	2	1.92%	Monitor BP
Amiodarone	Atorvastatin	Inhibition of CYP3A4-mediated atorvastatin metabolism	Increased risk of myopathy or rhabdomyolysis.	2	1.92%	Monitor creatine kinase (CK) levels
Ciprofloxacin	Zolpidem	Unknown	Increased zolpidem plasma concentrations.	2	1.92%	-
Amiodarone	Verapamil	Inhibition of CYP3A4-mediated metabolism of amiodarone	Increased plasma concentrations of amiodarone; increased risk bradycardia, sinus arrest, or AV block.	2	1.92%	Monitor HR

Factors Contributing to DRPs

A statistically significant difference (p=0.0232) between the age and DRP was observed. The average number of drugs prescribed was predominant in the age >60 years. A statistically significant difference (p=0.043) between the co-

morbities and DRPs was also observed. There was no statistically significant difference (p=0.240) between the stages of CKD with DRPs observed.

DISCUSSION AND CONCLUSION

It has been known that drugs may directly cause or contribute to hospital admission when the numbers of drugs are increased. DRPs can occur throughout the entire medication process and represent risk factors for ADRs and events [10]. Proper dosing can also have an economic impact on the health system. Dosage adjustment can result in avoidance of costs associated with drug related toxicity and in cost savings in terms of drug cost [11].

Majority of patients in our study population belonged to the age range 61-80 years, with highest number of DRPs (n=90) which was statistically significant. A study conducted by Lesley A .Stevens *et al*., [3], have also reported that chronic kidney disease was a substantial concern in the elderly population with an increasing incidence of treated kidney failure resulting in dialysis.

In this study, several co-morbidities were found and the major co-morbid conditions included Hypertension (37.10%), Diabetes mellitus (27.98%), Coronary Artery Disease (20.12%). This was concordant to the findings of the studies conducted by Lesley A. Stevens *et al*., Dena E. Rifkui *et al*., [12], in which they have reported that the high prevalence of CKD increased with obesity, Diabetes Mellitus , Cardiovascular drugs , Hypertension. As the age processes, co-morbid conditions increase and as a result number of prescribed drugs increase, eventually leading to increase in DRPs.

Polypharmacy can be considered as important factor for causing DRPs. In the present study, the average number of drugs per prescription was found to be 13.3 ± 3.53. A total of 163 DRPs were found with an average of 1.25 ±1.23 DRPs per prescription and the number of DRPs were found to be increasing with an increase in number of drugs per prescription. This is in accordance with the reports of the study conducted by Katie E Cardone *et al*., [13], which stated that CKD patients were prescribed an average of 12 medications and were at higher risk of DRPs.

In the present study, among the identified DRPs were Adverse drug reactions and Drug combinations to use with caution and need close monitoring (11.53%) were predominant, followed by overdose 12 (9.23%). This was in accordance with the reports of a study conducted by Leape *et al.*, [14], which reported ADEs was the most common cause. Increasing the knowledge and understanding of ADEs may help to prevent higher proportion of ADEs However in a study conducted by Manley et al. reported the major cause of DRP in CKD was medication dosing errors [15]. The proper dosing of medications for patients with renal impairment can maximize therapeutic efficacy and minimizes toxicity. In this study 15 ADRs, out of which 3 were probable and 12 were possible with respect to Naranjo Causality Assessment Scale. The ADRs observed were Clopidogrel & Heparin induced thrombocytopenia, Prazosin & (Isosorbide dinitrate+ Hydralazine) induced hypotension, Furosemide & Torsemide induced hypokalemia and hyponatremia respectively. There were relative contraindications found in this study includes Isosorbide mononitrate with Sildenafil, Fluconazole with Ivabradine/ Donepezil/ Quetiapine/ Amiodarone/ Ondansetron, Linezolid with Escitalopram, Itraconazole with Ivabradine respectively.

The other DRPs identified in our study were untreated indication 10 (7.69%) and Drug without indication 4 (3.08%). However a study conducted by Angeles Pardo Ropez *et al.*, [16] found 34.5% patients require additional treatment and 14.3% had a DRP of unnecessary treatment. In the present study, untreated indications found such as decreased Hb levels, increased uric acid levels and potassium levels and chronic H.pylori, gastritis.

The potential Drug interactions (80.0%) which means that there is a possibility of interactions but were not observed in these patients. Drug-Drug interactions can lead to decrease or increase in a drug effect; eventually causing sub-therapeutic or supra- therapeutic effect. These drug interactions should be closely monitored. To prevent these interaction the pharmacokinetic properties of each drug can be checked and if the half-lives of the drugs are not crossed over, they can be administered at different timings.

DRPs are common in patients with renal insufficiency maintained on haemodialysis [1]. In our study included 65 haemodialysis patients with 72 DRPs. Such patients are at higher risk, as they require complex therapeutic regimens with 5 or more medication doses per day that require frequent monitoring and dosage adjustment; they usually have other concurrent diseases including Diabetes Mellitus, Hypertension, Coronary Artery Disease and Infections.

Our study concludes that a direct proportionality was seen with number of drugs prescribed and DRPs. As observed with the increasing age and as such increase in comorbidities.

Monitoring the drug therapy for the occurrence of DRPs is a valuable way of preventing DRPs. This can be identified and reported to the physician to act and adjust drug regimens before adverse events arise and treatment failure occurs. Recognition and resolution

of DRPs will decrease drug related morbidity and mortality.

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