

Study on Medication Use Pattern and Prevalence of Potential Drug-Drug Interactions among Chronic Kidney Disease Patients

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ABSTRACT

Background

Chronic Kidney Disease (CKD) is a significant public health issue, due to its rising incidence, prevalence, and associated economic burden. Patients with chronic kidney disease frequently require the use of multiple medications due to their various comorbid conditions. When a patient takes multiple medications at the same time, there is a higher chance of drug-drug interactions (DDIs). This could be linked to higher rates of morbidity, mortality, length of hospital stays, and expense of medical care.

Objective

To evaluate the prevalence of potential drug-drug interactions and the medication use patterns among chronic kidney disease patients admitted to the nephrology unit.

Method

This study was conducted at a tertiary care hospital in western Nepal, where the data of 180 patients from the medical record section was collected who were previously admitted from January 2020 to December 2021 at the nephrology ward. The patient's demographic profile and medication prescribed were collected in the patients' data collection form and potential drug-drug interactions (pDDIs) were checked from the Medscape interaction checker. Data analysis was done from Microsoft Excel 2019 and Statistical Package for the Social Sciences (SPSS) version 20.

Result

A total of 1527 medicines were prescribed among 180 patients, the mean number of medicines per prescription was 8.5 ± 3.1 . The most commonly prescribed individual medicine was torsemide, ranitidine, and amlodipine. The prevalence of potential drug-drug interactions was 86.6%. Out of a total of 786 pDDIs, 4(0.5%) were contraindicated, 42(5.3%) were serious, and 527(67%) were moderate while 213(27.1%) were minor. The most frequently seen potential drug-drug interactions in our study were between sodium bicarbonate and ferrous salt in 36.1% of patients.

Conclusion

Chronic kidney disease patients in this study were prescribed with higher number of medications and the prevalence of potential drug-drug interactions was high.

KEY WORDS

Chronic kidney disease, Medication use pattern, Potential drug-drug Interaction

INTRODUCTION

Chronic Kidney Disease is a significant public health issue, due to its rising incidence, prevalence, and associated economic burden. The prevalence of CKD is 13.4% (11.7 - 15.1%) worldwide.¹ CKD is a major cause of mortality worldwide, disproportionately impacting low- and middle-income nations.² The prevalence of CKD in Nepal was 6.8%, according to the Nepal Health Research Council (NHRC) which was estimated from the year 2016 to 2018.³ A large number of comorbid conditions affect CKD patients, including underlying illnesses and side effects of kidney impairment.⁴

Due to the use of multiple medications to treat chronic kidney disease, there is a comparatively high prevalence of drug-drug interactions among them.⁵ It is linked to higher rates of morbidity, mortality, hospital stays, and medical expenses.^{6,7} According to earlier reports, CKD patients were more likely to have between 56.9% and 89.1% of pDDIs.⁸ A study found that drug-drug interactions (60%) were the most common drug-related problems in CKD patients.⁹ Letinier et al. found that admission of patients to the emergency department of a hospital was found among one percent of patients as a result of drug-drug interaction.¹⁰

However, little information is known regarding current practice patterns, the prevalence of polypharmacy, and risk factors, despite the acknowledged difficult circumstances of pharmacotherapy in CKD patients. Thus, the goal of this study was to evaluate the prevalence of pDDIs and the medication use patterns among CKD patients undergoing treatment at the nephrology unit.

METHODS

A retrospective, cross-sectional study was conducted at the nephrology unit of one of the medical colleges in Western Nepal. Data of 180 patients, who were admitted from 2020 January-2021 December, were collected from the medical record section. Patients 18 years or older who had been previously or currently diagnosed with CKD were included in the study. Ethical approval was obtained from the institutional review committee of Kathmandu University School of Medical Sciences, Dhulikhel (IRC-KUSMS 24/22). Permission for data collection was also obtained from the Universal College of Medical Science.

The medication regimens of patients were examined for pDDIs using the Medscape drug reference database.¹¹ The software recognizes and categorizes drug-drug interactions based on the clinical significance of each category. Drug interactions were categorized as Minor, Moderate, Serious, and contraindicated.

For medication use patterns, the World Health Organization–Anatomical Therapeutic Chemical (WHO-ATC) classification system was used.¹² The patient's sociodemographic data,

CKD stage, number and list of medications taken during hospital admission and number and list of comorbidities were all collected using an appropriate patient data collection form. Clinical records of the patients who met the inclusion criteria were used to gather their data. The glomerular filtration rate (eGFR) was determined using serum creatinine, and the National Kidney Foundation's eGFR calculator was used to stage CKD.¹³

Statistical analysis was done using SPSS version 20 and MS Excel- 2019. Descriptive analysis was conducted using frequencies for categorical variables, the mean, and the standard deviation for quantitative variables. Percentages of pDDIs by a patient were calculated to describe the prevalence of pDDIs. To identify the independent predictors of pDDIs, binary logistic regression was used. Exposure to pDDIs was regarded as a dependent variable in the model (0= absent, 1= present). In addition, the following factors were included in the model as predictors of pDDIs: gender (0= female, 1= male), age, number of prescribed drugs, hypertension (1= yes, 0= no), diabetes (1= yes, 0= no), Length of hospital stay, CKD stage (1= stage 5, 0= stage 1=4), and number of comorbidities.

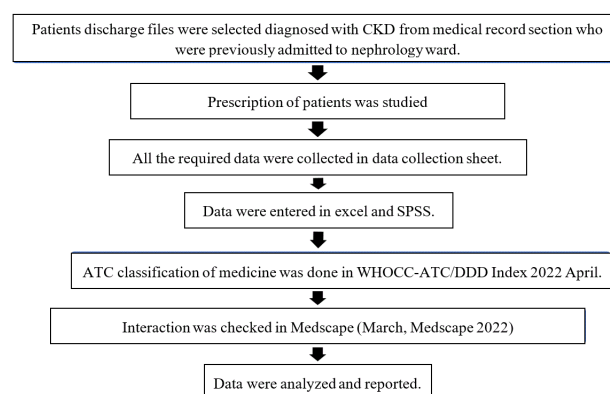


Figure 1. Flow chart of study method

RESULTS

A total of 180 patients' medical records diagnosed with CKD were included in the study. Majority of the patients were male 110(61.1%), aged between 30-60 years was 106(58.9%) with the mean age ($\pm$ SD) of 51.7 $\pm$ 16.1 years. More than half of the patients i.e. 122(67.8%) had 3-5 co-morbid conditions. Most of the patients had hypertension as a co-morbid condition in about 174(96.7%) of patients. Similarly, 166(92.2%) of patients had anemia, and 66(36.7%) of patients had diabetes mellitus as a co-morbidity. Table 1 represents the demographic and clinical characteristics of the patients.

Medication use pattern

A total number of 1527 medications and 134 different generic molecules of medicine were prescribed to 180 individuals,

Table 1. Demographic And Clinical Characteristics Of The Patients

Demographic characteristics		Frequency (%)
Gender	Male	110(61.1)
	Female	70(38.9)
Age (51.7500±16.1)	< 30	15(8.3)
	30-60	106(58.9)
	> 60	59(32.8)
CKD Class	G1	2(1.1)
	G2	1(0.6)
	G3b	2(1.1)
	G4	15(8.3)
	G5	160(88.9)
Hemodialysis	Yes	160(88.9)
	No	20(11.1)
Number of Co-morbid conditions	1-2	52(28.9)
	3-5	122(67.8)
	> 5	6(3.3)
Co-morbid conditions	Hypertension	174(96.7)
	Diabetes Mellitus	66(36.7)
	Asthma	5(2.8)
	COPD	15(8.3)
	Anemia	166(92.2)
	Pneumonia	17(9.4)
	Hyperlipidemia	27(15.0)
	Hypothyroid	18(10%)
	Pulmonary disease	18(10.0)
	Cardiac disease	10(5.6)
	Renal disease	19(10.6)
	Others	18(10.0)
Length of hospital stay (4.85±3.44)	1-3	90(50)
	4-5	27(15)
	> 5	63(35)
	< 5	35(19.4)
Total medicine prescribed (8.48±3.13)	5-8	65(36.1)
	9-12	57(31.7)
	> 12	23(12.8)

and the mean number of prescribed medications per patient was 8.5 ± 3.1 . A number of medicines in the range of 5-8 were given to the highest number of patients, i.e., 65(36.2%). Patients who were prescribed < 5 medication were 35(19.4%), 9-12 medications were 57(31.7%) and > 12 medication were 23(12.8%).

Patients were prescribed mostly from classes A (Alimentary Tract and Metabolism) and C (Cardiovascular System). A total of 161 patients i.e. 89.4%, were prescribed from each of these classes, whereas medication prescription was least from classes D, 2(1.1%). Patients were not prescribed from class L and S. Table 2 represents the prescription of the drug according to the ATC system.

Table 3. Most frequently prescribed medicine

Medications	Frequency (%) (n=180)
Torsemide	124(68.9)
Ranitidine	119(66.1)
Amlodipine	112(62.2)
Ferrous Sulphate + Folic Acid	82(45.6)
Sodium Bicarbonate	73(40.6)
Prazosin	70(38.9)
Erythropoietin	68(37.8)
Metoprolol	53(29.4)
Ceftriaxone	42(23.3)
Calcium Acetate	40(22.2)

The most commonly prescribed individual medicine was torsemide (68.9%), ranitidine (66.01%), amlodipine (62.2%) followed by ferrous sulfate + folic acid (45.06%), sodium bicarbonate (40.6%), prazosin (38.9%), erythropoietin (37.8%), metoprolol (29.4%), ceftriaxone (23.3%), calcium acetate (22.2%). Table 3, represents the most frequently prescribed medications.

Prevalence and Distribution of Potential Drug-Drug Interactions

Table 4. Prevalence of pDDIs

Potential drug-drug interactions		Frequency (%) (n=180)
No. of pDDIs (4.4±3.7)	No	24(13.3)
	1-5	93(51.6)
	6-10	51(28.3)
	11-15	10(5.6)
	> 15	2(1.1)
	Contraindicated	4(0.5)
Severity of pDDI	Serious	42(5.3)
	Moderate	527(67)
	Minor	213(27.1)

Prevalence of pDDIs

Among 180 patients who were in this study, 156(86.66%) patients had potential drug-drug interactions. It means the prevalence of pDDI was 86.6%. The prevalence rate was calculated by dividing the patients with pDDI by the total number of patients in the study and multiplying by 100.

Frequency and severity of pDDIs

154 different and a total of 786 pDDIs were identified. Similarly, 93(51.6%) patients showed 1-5 pDDIs, 51(28.3%) patients showed 6-10 pDDIs, 10(5.6%) showed 11-15 and 2(1.1%) had more than 15 pDDIs. According to Medscape drug-drug interaction checker, out of a total of 786 pDDIs, 4(0.5%) were contraindicated, 42(5.3%) were serious, and 527(67%) were moderate while 213(27.1%) were minor pDDIs. Table 4, represents the frequency and severity of pDDIs.

Mechanism of potential drug-drug Interaction

Most of the potential drug-drug interactions were pharmacodynamics i.e. 53%, and 35% were pharmacokinetics in nature. Similarly, 1% of interactions were physical incompatibility and 11% of interaction mechanisms were unknown. Figure 2, represents the mechanism of pDDIs.

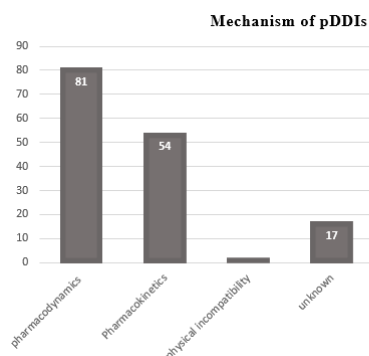


Figure 2. Mechanism of pDDIs

The severity of potential drug-drug interactions (pDDIs)

The most frequently seen pDDIs in our study was between sodium bicarbonate and ferrous salt. Cases of contraindicated interaction included prescriptions of ceftriaxone and calcium acetate and ceftriaxone and calcium gluconate. Noteworthy severe drug interactions included

clonidine + metoprolol, azithromycin + ondansetron, ondansetron + levofloxacin, sodium bicarbonate + levofloxacin, etc. Similarly, the most frequent moderate potential drug interactions included interaction between sodium bicarbonate + ferrous salt, torsemide + metoprolol, prazosin + amlodipine, and sodium bicarbonate + metoprolol. Minor drug interaction was torsemide + folic acid, torsemide + calcium acetate, calcium acetate + ferrous salt, amlodipine + hydrocortisone, clonidine + insulin, torsemide + clopidogrel. Table 5, represents the most frequent drug interaction during hospital stays.

Predictors of pDDIs

The number of prescribed medications and pDDIs were statistically significantly associated (OR-1.79). This suggests that the likelihood of pDDIs occurring among these CKD patients increases as the number of medications prescribed increases. Additionally, there was a statistically significant association between the respondents' CKD stage (OR-3.83) and the occurrence of DDIs. This suggests that as the CKD stage increases, pDDIs incidence rises as well. Table 6 shows Binary Logistic regression to find the predictors of pDDIs.

DISCUSSIONS

This study reported the medication use pattern and prevalence of potential drug-drug interactions among

Table 2. Table 4 Most frequent drug interaction during hospital stays¹¹

Drug Interaction	N	Mechanism	Type	Outcome	Severity
Ceftriaxone + Calcium Gluconate	2	Physical incompatibility	-	Particulate precipitation risk in the kidney and lungs, which could be fatal.	Contra-indicated
Ceftriaxone + Calcium acetate	2	-	-	Particulate precipitation risk in the kidney and lungs, which could be fatal.	Contra--indicated
Clonidine + metoprolol	8	Pharmacodynamic	Synergism	Either make the other more toxic. Atrioventricular block and sinus node dysfunction could get worse as a result of additive sympatholytic action.	Serious
Azithromycin + Ondansetron	5	Pharmacodynamics	Additive	Both increase the QTc interval.	Serious
Ondansetron + Levofloxacin	5	Pharmacodynamic	Additive	Effects on QT interval prolongation	Serious
Sodium Bicarbonate + Levofloxacin	3	Pharmacokinetics	Absorption	Sodium bicarbonate decreases the level of levofloxacin	Serious
Sodium Bicarbonate + Ferrous Salt	65	Pharmacokinetics	Absorption	Ferrous sulfate's concentration or effects will be lessened by sodium bicarbonate.	Moderate
Torsemide + Metoprolol	51	Pharmacodynamic	Antagonism	Metoprolol increases and torsemide decreases serum potassium.	Moderate
Prazosin + Amlodipine	44	Pharmacodynamic	Synergism	Both increase anti-hypertensive channel blocking	Moderate
Sodium Bicarbonate + Metoprolol	40	Pharmacokinetics	Absorption	Sodium bicarbonate will decrease the level of metoprolol	Moderate
Torsemide + Folic Acid	59	Pharmacokinetics	Elimination	Torsemide decreases the level of folic acid	Minor
Torsemide + Calcium Acetate	42	Pharmacokinetics	Elimination	Torsemide decreases the level of calcium acetate	Minor
Calcium Acetate + Ferrous Salt	35	Pharmacokinetics	Absorption	Ferrous salt increases the level of calcium acetate	Minor
Amlodipine + Hydrocortisone	7	Pharmacokinetics	Metabolism	Amlodipine's effectiveness or level will be reduced by hydrocortisone.	Minor
Clonidine + Insulin	5	pharmacodynamics	Antagonism	Clonidine decreases the effects of insulin	Minor
Torsemide + Clopidogrel	5	Pharmacokinetics	Metabolism	Clopidogrel increases level of torsemide	Minor

Table 6. Binary Logistic regression to find the predictors of pDDIs.

Independent variables		OR (Odds Ratio)	95% C.I. Lower- Upper	P- Value
Age		0.97	0.94-1.01	0.21
No. of Co-morbidities		1.82	0.96-3.46	0.26
Length of hospital stay		0.79	0.63-1.00	0.06
No. of Medicine		1.79	1.34-2.38	0.00*
Gender	Female (Ref)	1		
	Male	1.19	0.39-3.62	0.75
Hypertension	No (Ref)	1		
	Yes	5.19	0.76-35.2	0.09
Diabetes Mellitus	No (Ref)	1		
	Yes	0.61	0.15-2.44	0.49
CKD stage	Stage G1-G4 (Ref)	1		
	Stage G5	3.83	1.05-13.83	0.04*

chronic kidney disease patients at a tertiary care hospital in Nepal, which included a total of 180 patients. The mean ($\pm$ SD) prescribed medicine in this study was 8.5 ± 3.1 . The result of this study is a bit more than the study conducted in Malaysia, which reported a mean ($\pm$ S.D) of 7.87 ± 2.44 medications.¹⁴ While this result is lower than the study conducted by Rama et al. which reported a mean ($\pm$ SD) of 12.08 ± 6.30 medications.¹⁵ This overall suggests that polypharmacy is common in CKD patients, which is the risk factor for pDDIs. This may be because CKD patients have multiple co-morbid conditions and complications.

Our study showed a higher number of medications prescribed were from class A (alimentary tract and metabolism) and C (Cardiovascular drugs) i.e. 89.4% of patients, according to the ATC classifications system. Torsemide, ranitidine, amlodipine, ferrous sulfate + folic acid, and sodium bicarbonate were the most frequently prescribed medications in this study. Likewise, the most commonly prescribed drugs in research conducted in Nigeria were furosemide, lisinopril, and calcium carbonate.¹⁶ Another study conducted by Santos-Díaz et.al revealed that omeprazole, acetaminophen, salicylic acid, bisoprolol, furosemide, and allopurinol were the most frequently prescribed medications.¹⁷

Torsemide, a loop diuretic was prescribed to treat sodium retention, volume expansion, and hypertension.¹⁸ Ranitidine was the second most prescribed medication in our study for stress-ulcer prophylaxis. However, a study had identified ranitidine as a potentially inappropriate medication in elderly patients with advanced CKD. The research also suggested not to use ranitidine without dose adjustment because renal function impairment is associated with increased plasma ranitidine level.¹⁹ Similarly, amlodipine was the safest antihypertensive drug for CKD patients and it is highly prescribed to treat hypertension in our study.²⁰

Ferrous sulphate had been prescribed for treating anemia.²¹ Likewise, sodium bicarbonate may slow kidney function decline and potentially enhance vascular endothelial function in CKD patients.²² This overall implies that most of the prescribed drugs in our study treat complications which arise in the advanced CKD stage.

In this study, the prevalence of pDDIs was 86.6% during hospitalization. However, the result of our study is higher than the study conducted by Sgnaolin et al. i.e., 56.91%.²³ Similarly, Rama et al. reported 76.9%, and Saleem et al. reported a 78.5%, prevalence of pDDIs.^{15,24} Likewise, the reported prevalence in our study is lower than Al-Ramahi et al. which reported (89.1%) pDDIs.²⁵ The methodology, interaction software, average number of drugs per prescription, and stage of CKD may be the possible reasons for variations in the prevalence rates of pDDIs in the research.²⁶

Our study showed 4(2.2%) patients with contraindicated pDDIs, 27(15%) with serious, 145(80.6) with moderate pDDIs which requires monitoring closely, and 101(56.1%) patients with minor pDDIs. The majority of the drug interactions were of moderate severity which was a common finding in the previous studies.^{15,27,28} In this study, the prevalence of contraindicated interaction was 0.5%, which was only observed in four patients, which is comparable to 0.4% reported by Marquito et al.²⁸

Polypharmacy is the primary cause of pDDIs and to reduce this issue, rational prescribing should be implemented.²⁹ Additionally, to ensure that patients use medications intelligently, doctors and pharmacists should better educate patients about these potential interactions.¹⁴ Monitoring possible DDIs may encourage rational prescribing and dispensing and may highlight the need for education centred on appropriate prescribing.³⁰ Along with encyclopedias, journals, textbooks, and the internet, hospitals' pharmacies ought to have electronic drug interaction tools as well. More studies should be done to reduce the frequency of harmful drug interactions, especially those that could result in nephrotoxicity.³¹

Patients receiving multiple drug therapies frequently experience pharmacokinetic and pharmacodynamic types of drug interactions.³² Our study found higher pharmacodynamic interactions, and Comparable to our study, research by Shahzadi et al. found higher pharmacodynamic pDDIs i.e. (49%), than pharmacokinetic (42.94%).³³

Contraindicated drug interactions in this study were between calcium gluconate and ceftriaxone. Sever potential drug interaction was between clonidine and metoprolol which was also similar to the study conducted by Rama et al.¹⁵ Similarly, the interaction between azithromycin and ondansetron, ondansetron and levofloxacin, sodium bicarbonate, and levofloxacin were also similar to these studies.^{34,35}

The most frequently seen pDDIs in our study was between sodium bicarbonate and ferrous salt in 36.1% of patients. A study conducted at a tertiary care medical hospital in India also demonstrated the interaction between sodium bicarbonate and ferrous salt as the most common pDDIs.²⁷ A report from this study, however, is different from those from Rama et al. and Al-Ramahi et al. Ascorbic acid and cyanocobalamin were listed by Rama et al. as the most frequent interactions, while CaCO₃ and amlodipine were listed by Al-Ramahi et al.^{14,15} One of the factors contributing to the occurrence of drug interactions is polypharmacy. When a person uses five or more medications simultaneously each day, it leads to polypharmacy. However, CKD patients have multiple comorbid conditions, necessitating the use of numerous medications.⁸

Each patient, in our study, took a mean of 8.5 ± 3.1 medications as part of their drug regimen, which undoubtedly increased their risk of a drug interaction. Similarly, in our studies, all the patients were diagnosed with at least one comorbid condition. The higher the comorbid condition higher the chance of polypharmacy which ultimately leads to pDDIs. The Advanced CKD stage is also one of the factors that result in prescribing a higher number of drugs since patients with CKD stage V are at risk of multiple co-morbid diseases than stage I.²⁶

Comparing the findings here with different studies we can find variations among the results. A statistically significant association between the number of prescribed medications and the occurrence of pDDIs was found by Fasipe et al.¹⁶ This suggests that, among CKD patients, the likelihood of developing DDIs rises with the increasing number of prescribed medications. Al-Ramahi et al. also showed a statistically significant correlation between age and the number of potential interactions. The number of chronic illnesses and the total number of medications that the patients took were also related to the number of pDDIs.²⁵ This overall implies that patients with CKD have multiple co-morbid conditions, which makes them necessitating to take multiple medicines to treat the co-morbid conditions,

which increases the risk of drug interactions. Thus, it is recommended to document all the prescribed drugs for CKD patients and screen for potential drug interactions.

The study's theoretical discovery of pDDIs, which may not clinically manifest, was its main theoretical limitation. Our study made use of the free and convenient Medscape interaction checker software, which was available in our settings. The software only permitted the checking of two drugs. The software did not have the option to check interactions related to doses, even though some interactions are dose-dependent. The software program assumed that two drugs would be taken at the same time and did not account for the interval between drug administration. The result of the interaction and the medical professional's strategy in the occurrence of adverse drug reactions associated with pDDIs were not documented. However, this study has highlighted the scope of possible DDIs among CKD patients and the necessity of taking preventative measures to lessen these extra burdens on patients.

CONCLUSION

The prevalence of pDDIs is high among CKD patients. Torsemide, ranitidine, amlodipine, and sodium bicarbonate were the most frequently prescribed medications. Most of the drug interactions were of moderate severity. The major predictors of drug-drug interactions were the number of prescribed medications and the advanced CKD stage. The most common drug interactions were between sodium bicarbonate and ferrous salt. The high prevalence of pDDIs in CKD patients is a serious problem since it affects their quality of life, morbidity, and mortality. It may be necessary for doctors, clinical pharmacists, and other healthcare providers to work in an interdisciplinary manner to closely monitor patients' prescriptions to detect, avoid, and address any undesired drug interactions. Additionally, using the available interaction software to identify and steer clear of dangerous pDDIs is advised.

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