

Clinical relevancy and determinants of potential drug–drug interactions in chronic kidney disease patients: results from a retrospective analysis

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Background: Chronic kidney disease (CKD) alters the pharmacokinetic and pharmacodynamic responses of various renally excreted drugs and increases the risk of drug-related problems, such as drug–drug interactions.

Objectives: To assess the pattern, determinants, and clinical relevancy of potential drug–drug interactions (pDDIs) in CKD patients.

Materials and methods: This study retrospectively reviewed medical charts of all CKD patients admitted in the nephrology unit of a tertiary care hospital in Pakistan from January 2013 to December 2014. The Micromedex Drug-Reax[®] system was used to screen patient profiles for pDDIs, and IBM SPSS version 20 was used to carry out statistical analysis.

Results: We evaluated 209 medical charts and found pDDIs in nearly 78.5% CKD patients. Overall, 541 pDDIs were observed, of which, nearly 60.8% patients had moderate, 41.1% had minor, 27.8% had major, and 13.4% had contraindicated interactions. Among those interactions, 49.4% had good evidence, 44.0% had fair, 6.3% had excellent evidence, and 35.5% interactions had delayed onset of action. The potential adverse outcomes of pDDIs included postural hypotension, QT prolongation, ceftriaxone–calcium precipitation, cardiac arrhythmias, and reduction in therapeutic effectiveness. The occurrence of pDDIs was found strongly associated with the age of <60 years, number of prescribed medicines ≥ 5 , hypertension, and the lengthy hospitalization of patients.

Conclusion: The occurrence of pDDIs was high in CKD patients. It was observed that CKD patients with an older age, higher number of prescribed medicines, lengthy hospitalization, and hypertension were at a higher risk of pDDIs.

Keywords: potential drug–drug interactions, interactions, CKD, pharmacist, clinical pharmacy, DDI, drug interaction, chronic kidney disease, Pakistan

Introduction

Chronic kidney disease (CKD) is one of the major challenges that affects ~8%–16% of the population worldwide.^{1,2} If patients with compromised renal function get some secondary complication, then risk assessment becomes essential to avoid any hazardous or damaging effects on the kidneys.³ In the case of negligence, the damaging or unwanted effects may appear in the form of adverse drug reactions, idiosyncratic reactions, hypersensitive reactions, or drug–drug interactions (DDIs).⁴ “A DDI means a phenomenon by which a drug potentiates or diminishes the effect of other drugs by pharmacokinetics, pharmacodynamics, or various other mechanisms”.⁵

Drug-related problems, such as DDIs, are one of the major therapeutic challenges for the treatment of inpatients, especially for those who are suffering from CKD, due

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to its complex nature.⁶ Various studies done in developing countries have revealed that the chances of DDIs are present in ~11.0% of patients, rising to 40.0% among patients taking five drugs, and 80.0% in patients with more than five medicines.⁷ Earlier studies also report that ~74.9% of CKD patients may have one or more potential DDI (pDDI).⁸

DDI studies are being widely performed worldwide.^{7,9} These studies are being conducted particularly in those clinical settings where the pharmaceutical services departments are well established and clinical pharmacists are efficiently monitoring and making individual patients' therapy safe and cost-effective by making different interventions.^{7,10,11}

CKD is highly prevalent in Pakistan when compared with other chronic noncommunicable diseases and affects ~12.5% (11.4%–13.8%) of the population.¹² The majority of Pakistani public sector hospitals are fully funded by the government, and medical care and medicines are provided free-of-charge to both inpatients and outpatients.¹³ However, in spite of these benefits, inappropriate prescribing and occurrence of DDIs remain a big challenge to the health care system in Pakistan.^{14–16} In addition, the majority of public sector hospitals are lacking a well-developed clinical pharmacy setup and, to the best of our knowledge, there is an insufficiency of data on the pattern, determinants, and clinical relevancy of DDIs in CKD patients in Pakistan. Therefore, this study is conducted to assess the pattern, determinants, and clinical relevancy of pDDIs in Pakistani CKD patients.

Materials and methods

Study design and setting

This retrospective study was carried out in a nephrology unit of Bahawal Victoria Hospital (BVH), which is a 1600-bed tertiary care hospital located in Bahawalpur, Punjab, Pakistan. Bahawalpur is a district headquarter with an estimated population of 2,433,091 composed of 52.6% males and 72.6% population lives in rural areas.¹⁷ However, due to a lack of health care facilities in Bahawalpur, BVH is the only tertiary care teaching hospital throughout the district, which serves a huge population and caters for a high patient burden.

Sampling and data collection

During this study, the medical charts of CKD patients admitted in the nephrology unit of BVH from January 2013 to December 2014 were evaluated. Demographic and clinical data such as the gender, age, length of hospital stay, CKD stage, comorbidity, and the treatment provided were collected.

Assessment of pDDIs

The Micromedex Drug-Reax System (Thomson Reuters Healthcare Inc., Greenwood Village, CO, USA)¹⁸ was used to evaluate the occurrence of pDDI in CKD patients. Micromedex is a drug-specific pDDIs-detecting software, which possesses sufficient sensitivity ($\geq 83\%$) and specificity ($\geq 90\%$) to detect DDIs.^{19,20} In addition, this software was used to measure the mechanism and potential adverse outcomes of pDDIs. All of the identified pDDIs were classified based on their severity, onset of action, and documented evidence, and tables were generated. These levels are described in the Micromedex Drug-Reax System,¹⁸ as shown in Box 1.

Statistical analysis

Descriptive statistics was applied to evaluate patient characteristics. Logistic regression was applied to identify the association between the pDDIs and the patient characteristics. In the model, the exposure to pDDIs was considered dependent variable (0=absent, 1=present). Further variables used in the model as predictors of pDDIs were as follows: gender (1=female, 2=male), age (1=<60 years, 2= ≥ 60 years), number of prescribed drugs (1=<5, 2= ≥ 5), length of hospitalization (1=<5 days, 2= ≥ 5 days), CKD stage (1=stages 1–3, 2=stages 4–5), diabetes (1=Yes, 2=No), and hypertension (1=Yes, 2=No). The Hosmer–Lemeshow test was used to check the goodness-of-fit of the model and a *p*-value of ≤ 0.05 was

Box 1 Micromedex adapted classification about the type of onset, severity, and evidence of pDDI

Type of onset

Rapid: effect may occur within 24 hours.

Delayed: the effect may occur after 24 or more hours.

Severity of pDDI

Contraindicated: the drug combination cannot be used concurrently.

Major: more risk of permanent damage or even death and/or require medical intervention.

Moderate: the interaction may deteriorate patient's condition and may require alteration of therapy.

Minor: interaction do not impair therapeutic outcome and not require change in therapy.

Evidence of pDDI

Excellent: the interaction has been clearly demonstrated in well-controlled studies.

Good: studies strongly suggest that the interaction exists; however, proof of well-controlled studies is lacking.

Fair: available evidence is poor, but clinicians suspect the interaction on the basis of pharmacologic considerations or evidence is good for an interaction of pharmacologically similar drug.

Poor: theoretically, the interaction may occur but reports are very limited, such as few case reports.

Unlikely: data are very poor and lack a pharmacological basis.

Abbreviation: pDDI, potential drug–drug interaction.

considered statistically significant. IBM Statistical Package for the Social Sciences (SPSS) version 20 was used to carry out all statistical analyses.

Ethical approval

The study was approved by the Pharmacy Research Ethics Committee (PREC) of the Department of Pharmacy, The Islamia University of Bahawalpur, Pakistan. Patient consent to review their medical records could not be obtained due to the lack of patients' contact details at the concerned hospital. To satisfy PREC, approval was obtained from the administration of concerned hospital to access and use the un-anonymized and de-identified data.

Results

In total, 209 medical charts of CKD patients were evaluated. Of them, the majority (60.8%) were males. The majority of the patients were aged between 20 and 40 years, and the mean age of the patients was 38.34 years with a standard deviation of ± 16.82 . About 74.2% of the patients had CKD stage 5. More than half of the patients (65.1%) had a length of hospitalization >5 days. Diabetes and hypertension were present in 18.2% and 69.9% patients, respectively, and nearly 78.0% of the patients were prescribed more than five medicines (Table 1).

In terms of prevalence, nearly 541 pDDIs were observed in 164 (78.5%) CKD patients, of which 60.8% patients had

Table 1 Characteristics of chronic kidney disease patients

Variables	Frequency	Percentage
Gender		
Male	127	60.8
Female	82	39.2
Age (years)		
<20	33	15.8
20–40	94	45.0
41–60	60	28.7
>60	22	10.5
Length of hospital stay (days)		
<5	73	34.9
≥ 5	136	65.1
Number of prescribed medicines		
<5	46	22.0
≥ 5	163	78.0
Stage of chronic kidney disease		
1	1	0.5
2	3	1.4
3	19	9.1
4	31	14.8
5	155	74.2
Comorbidity		
Diabetes	38	18.2
Hypertension	146	69.9

Table 2 Prevalence and levels of potential drug–drug interactions (pDDIs) in chronic kidney disease patients

Type of prevalence	Patient, n (%)	Levels	Frequency, n (%)
Overall prevalence ^a	164 (78.5)	Total pDDIs	541 (100.0)
Severity of pDDIs^b		Severity	
Contraindicated	28 (13.4)	Contraindicated	30 (5.5)
Major	58 (27.8)	Major	75 (13.9)
Moderate	127 (60.8)	Moderate	306 (56.6)
Minor	86 (41.1)	Minor	130 (24.0)
Number of pDDIs per patient		Evidence	
1–2	81 (38.8)	Excellent	34 (6.3)
3–5	58 (27.8)	Good	267 (49.4)
≥ 6	25 (12.0)	Fair	240 (44.3)
Median	3	Onset	
Range	1–22	Rapid	187 (34.6)
Total pDDIs	541	Delayed	192 (35.5)
		Not specified	163 (29.9)

Notes: ^aOverall prevalence means the presence of at least one pDDI regardless of severity type; ^b percentages do not add up to 78.5% because many patients were exposed to multiple pDDIs of different severities.

moderate, 41.1% had minor, 27.8% had major, and nearly 13.4% patients had contraindicated interactions. Nearly 137 different drug interacting combinations were observed. Further analysis revealed that 49.4% pDDIs had good evidence, 44.3% had fair evidence, 6.3% had excellent evidence, and the majority of interaction (35.5%) had delayed onset of action (Table 2). It was also observed that 306 moderate pDDIs of 541 accounted for 56.2% of all pDDIs (Table 2).

The pDDIs observed in this study are given in Table 3. The majority of CKD patients were hypertensive; therefore, a separate table was also generated to highlight frequently occurring interactions in hypertensive CKD patients (Table 4). Logistic regression was applied, and predictors of pDDIs with a *p*-value of <0.1 in univariate analysis were further evaluated. The multivariate analysis of predictors revealed that gender (odds ratio [OR]=1.65; 95% confidence interval [CI]=0.9–3.2; *p*=0.136) was not associated with the occurrence of pDDIs. However, a significant association was observed with the age of <60 years (OR=0.3; 95% CI=0.1–0.8; *p*=0.019), length of hospital stay ≥ 5 days (OR=2.4; 95% CI=1.1–5.0; *p*=0.024), presence of a comorbidity such as hypertension (OR=3.0; 95% CI=1.2–7.5; *p*=0.017), and number of prescribed drugs ≥ 5 (OR=6.8; 95% CI=3.1–15.1; *p* <0.001). The details are shown in Table 5.

Discussion

To the best of our knowledge, this was the first study of its kind conducted at a tertiary care public sector hospital in Bahawalpur, which is a comparatively less developed district than others in Punjab province, Pakistan. The consequences

Table 3 Most frequently occurring major, moderate, and contraindicated interactions, their levels, and potential adverse outcomes

Interaction	Frequency	Percentage	Severity	Evidence	Onset	Potential adverse outcomes
Ferrous sulfate + omeprazole	34	5.8	Moderate	Good	Rapid	Reduced non-heme iron bioavailability
Calcium/vitamin D + ciprofloxacin	28	4.8	Moderate	Good	Rapid	Decreased ciprofloxacin efficacy
Captopril + furosemide	24	4.1	Moderate	Good	Rapid	Postural hypotension
Calcium gluconate + ceftriaxone	21	3.6	Contraindicated	Good	Not specified	Formation of ceftriaxone–calcium precipitates
Ciprofloxacin + ferrous sulfate	17	2.9	Moderate	Fair	Rapid	Decreased ciprofloxacin effectiveness
Amlodipine + atenolol	13	2.2	Moderate	Good	Rapid	Hypotension and/or bradycardia
Amlodipine + ciprofloxacin	12	2.0	Moderate	Fair	Not specified	Increased amlodipine exposure
Amlodipine + prednisolone	11	1.9	Moderate	Fair	Not specified	Reduced amlodipine efficacy
Furosemide + lisinopril	11	1.9	Moderate	Good	Rapid	Postural hypotension
Atenolol + prazosin	10	1.7	Moderate	Good	Rapid	Exaggerated hypotensive response
Ciprofloxacin + metronidazole	9	1.5	Major	Fair	Not specified	Increased risk of QT-interval prolongation and arrhythmias
Aspirin + calcium/vitamin D	8	1.4	Moderate	Fair	Delayed	Decreased salicylate effectiveness
Ciprofloxacin + prednisolone	8	1.4	Moderate	Excellent	Delayed	Increased risk of tendon rupture
Amlodipine + carbamazepine	6	1.0	Major	Fair	Not specified	Decreased exposure of amlodipine
Amlodipine + aspirin	6	1.0	Moderate	Good	Delayed	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect
Aspirin + sodium bicarbonate	6	1.0	Moderate	Fair	Delayed	Decreased salicylate effectiveness
Metronidazole + moxifloxacin	5	0.9	Major	Fair	Not specified	Increased risk of QT-interval prolongation and arrhythmias
Aspirin + insulin human regular	5	0.9	Moderate	Fair	Not specified	Increased risk of hypoglycemia
Carbamazepine + omeprazole	5	0.9	Moderate	Good	Delayed	Increased risk of carbamazepine toxicity
Enalapril + furosemide	5	0.9	Moderate	Good	Rapid	Postural hypotension
Amlodipine + simvastatin	4	0.7	Major	Good	Rapid	Increased simvastatin exposure and increased risk of myopathy, including rhabdomyolysis
Lisinopril + spironolactone	4	0.7	Major	Good	Delayed	Hyperkalemia
Atorvastatin + clopidogrel	4	0.7	Moderate	Excellent	Not specified	High on-treatment platelet reactivity
Carbamazepine + ciprofloxacin	4	0.7	Moderate	Fair	Not specified	Increased carbamazepine exposure
Ferrous sulfate + moxifloxacin	4	0.7	Moderate	Good	Rapid	Decreased moxifloxacin effectiveness
Furosemide + insulin human regular	4	0.7	Moderate	Fair	Not specified	Increased hyperglycemia risk; increased insulin requirement
Calcium acetate + ceftriaxone	3	0.5	Contraindicated	Good	Not specified	Formation of ceftriaxone–calcium precipitates

of drug-related problems, such as, DDIs, can potentially complicate the nature and severity of an illness such as CKD that itself requires multiple and complex therapeutic regimens.^{21,22} To ensure rational prescribing in high-risk patients, it is necessary to evaluate and identify the factors causing DDIs before any adverse outcome occurs.

The incidence of pDDIs identified in this study is 78.5%. This incidence is much higher than a Malaysian study in which a sample of 308 patients was taken, of which only 154 patients had confirmed CKD diagnosis and the reported incidence of pDDIs was 19.4%. The lower pDDI rate in a Malaysian study could be due to their lower sample size.²³ Marquito et al⁸ reported 74.9% pDDIs prevalence in Brazilian CKD patients, of which ~54.7% were males and the majority were aged ~70 years. Similarly, the prevalence of pDDI

was reported as 76.1% in an Indian study.²⁴ Hence, although variations exist in study designs of previous studies, a high prevalence of pDDIs has been observed in CKD patients, which supports our study findings.

Earlier studies reported a high incidence of pDDI in Pakistan, especially in pediatric patients,²⁵ internal medicine ward patients,²⁶ psychiatry patients,⁹ and cardiac patients.²⁷ The cumulative findings of these studies suggest that the prevalence of pDDIs may range from 25.8% to 91.1% in Pakistan.^{9,25,27} The published literature suggests that CKD mainly affects the older population, that is, at high risk of adverse drug effects due to multiple comorbidities such as diabetes and hypertension, and especially when they are prescribed multiple therapies or even a single drug, due to various pharmacokinetic reasons.²⁸

Table 4 Most commonly occurring drug interactions in hypertensive chronic kidney disease patients

Interacting pair	Frequency	Percentage
Ferrous sulfate + omeprazole	27	5.8
Calcium/vitamin D + ciprofloxacin	21	4.5
Captopril + furosemide	21	4.5
Calcium gluconate + ceftriaxone sodium	16	3.4
Calcium gluconate + ferrous sulfate	14	3.0
Ciprofloxacin + ferrous sulfate	14	3.0
Amlodipine + atenolol	13	2.8
Atenolol + prazosin	10	2.2
Amlodipine + prednisolone	9	1.9
Amlodipine + ciprofloxacin	8	1.7
Aspirin + calcium/vitamin D	8	1.7
Ciprofloxacin + metronidazole	7	1.5
Furosemide + lisinopril	7	1.5
Amlodipine + aspirin	6	1.3
Amlodipine + carbamazepine	6	1.3
Aspirin + sodium bicarbonate	6	1.3
Aspirin + insulin human regular	5	1.1
Ciprofloxacin + prednisolone	5	1.1
Amlodipine + simvastatin	4	0.9
Atorvastatin + clopidogrel	4	0.9
Carbamazepine + ciprofloxacin	4	0.9
Carbamazepine + omeprazole	4	0.9

Notes: The frequency and percentage depicted in the table is based on total 465 interactions that were observed in hypertensive chronic kidney disease patients.

This study showed that ~60.8% of pDDIs were moderate and 41.1% were minor. These are higher than an Indian study, which reported 57.0% moderate pDDIs and only 23.2% minor pDDIs.²⁴ The relatively high incidence of pDDIs in a Pakistani hospital is perhaps due to some potential barriers, such as the unavailability of clinical pharmacy staff, lack of multidisciplinary teams, lack of patient centeredness, shortage of time and overburden on physicians, and may be poor knowledge of the medical staff to identify pDDIs in usual clinical practice.²⁹

The majority of the pDDIs identified in this study are of moderate and minor severity. A few interactions with serious and contraindicated severity have also been observed, which have considerable potential to deteriorate patients' clinical condition, if left unmanaged (Tables 2 and 3). We observed that the pDDIs identified in this study are not specific only to CKD patients. Some interactions, such as furosemide + lisinopril, captopril + furosemide, and aspirin + insulin, have also been observed in internal medicine ward patients who were suffering from stroke, pyrexia, gastroenteritis, congestive heart failure, malaria, anemia, tuberculosis, ischemic heart disease, liver cirrhosis, pneumonia, meningitis, and urinary tract infection.²⁶

Table 5 Predictors of potential drug–drug interactions in chronic kidney disease (CKD) patients

Variables	Patients (n=209)		Univariate		Multivariate	
	Interaction present, n (%)	Interaction absent, n (%)	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Gender						
Male	104 (81.9)	23 (18.1)	1.65 (0.9–3.2)	0.136	–	–
Female	60 (73.2)	22 (26.8)				
Age (years)						
<60	150 (80.2)	37 (19.8)	0.4 (0.2–0.9)	0.012	0.3 (0.1–0.8)	0.019
≥60	14 (63.6)	8 (36.4)				
Hospital stay (days)						
<5	48 (65.8)	25 (34.2)	3.0 (1.5–5.9)	0.001	2.4 (1.1–5.0)	0.024
≥5	116 (85.3)	20 (14.7)				
Number of drugs						
<5	23 (50.0)	23 (50.0)	6.4 (3.1–13.3)	<0.001	6.8 (3.1–15.1)	<0.001
≥5	141 (86.5)	22 (13.5)				
CKD stage						
1–3	15 (65.2)	8 (34.8)	0.5 (0.2–1.2)	0.107	–	–
4–5	149 (81.0)	37 (19.9)				
Diabetes						
Yes	33 (86.8)	5 (13.2)	2.0 (0.7–5.5)	0.172	–	–
No	131 (76.6)	40 (23.4)				
Hypertension						
Yes	121 (82.9)	25 (17.1)	2.3 (1.1–4.5)	0.020	3.0 (1.2–7.5)	0.017
No	43 (68.3)	20 (31.7)				

Notes: Hosmer–Lemeshow goodness-of-fit test: $p=0.65$. Data in bold indicates statistical significance (P -value<0.05) obtained after statistical analysis.

Abbreviations: OR, odds ratio; CI, confidence interval.

We suggest that the consequences of pDDIs should be considered carefully because some interactions that appear in the pDDI checking software do not occur in usual practice, that is, calcium gluconate + ceftriaxone interaction takes places only in the infusion bag, if mixed together. But if given separately (oral calcium and IM/IV ceftriaxone), then there is no need to worry.³⁰ Therefore, it should be kept in mind that the various drug-screening software including Drug-Reax System provide only an instant computerized drug interaction contents, which should be assessed carefully by the clinical pharmacists. To understand pDDIs carefully, physicians should consult pharmacists while prescribing drugs to CKD patients and seek their expertise to avoid over or underestimation of the clinical relevancy of pDDIs.

Finally, the findings such as the associations of pDDIs with the lengthy hospitalization, higher number of medicines prescribed, and the un-association of pDDIs with the gender are in line with previous studies.^{26,27} However, to the best of our knowledge, the findings such as the association of pDDIs with an age of <60 years and hypertension were not reported before. We also tried to study the impact of CKD stage and diabetes on the occurrence of pDDI, but the multivariate analysis confirmed that there was no such association. Further research can be conducted to answer this question using a large and multicenter data. Moreover, research should be done to identify various other factors, such as the use of a particular drug class, multiple prescribers, disease diagnosis, and the type and number of comorbid illnesses.

Conclusion

The prevalence of pDDIs is high in CKD patients in Pakistan. The determinants of pDDIs are the age of <60 years, length of hospital stay ≥ 5 days, presence of hypertension, and the number of prescribed medications ≥ 5 . The higher occurrence of pDDIs in our study setting reflects the lack of knowledge in prescribers about detecting pDDIs and indicates the importance of clinical pharmacy staff that can help in managing and reducing pDDIs in CKD patients. To make pDDIs screening more effective, both clinical pharmacists and physicians are advised to work in a more collaborative manner.

Clinical implications and recommendations

The DDIs are a major challenge to the effective management of hospitalized CKD patients. The majority of the pDDIs identified in this study are of moderate and minor severity and lack of clinical relevancy which reflects that nephrologists are prescribing somewhat rationally. However, a few severe and contraindicated interactions have also been observed that

have a considerable potential to deteriorate patients' clinical condition, if left unmanaged. The occurrence of major and contraindicated interactions in CKD patients indicates the need of clinical pharmacy staff at nephrology units of hospitals. In terms of practice, except for the major pDDIs, the moderate and severe DDIs are usually not considered. To make prescribing safer, careful understanding about pDDIs even for a minor or moderate severity is important. In addition, as this study showed that CKD patients who are in the age of <60 years, experience a lengthy hospital stay, have hypertension, and are on multiple therapies are at more risk of pDDIs. Therefore, physicians and pharmacists should take care of patients who fall under these categories. We advise pharmacists to play their role wisely in Pakistani tertiary level hospitals in a more collaborative way to reduce work burden on physicians and ensure the quality use of medicines.

Study limitations

The potential limitations of this study are as follows: first, the actual adverse effects or outcomes of the identified pDDIs could not be studied due to the lack of stored data in the hospital concerned. Therefore, further studies should be conducted to evaluate the actual and clinical consequences of pDDIs in CKD patients. Second, due to a lack of funding, this study was carried out in only one public sector tertiary care teaching hospital; therefore, these study findings should be carefully generalized across the Pakistan.

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Disclosure

The authors report no conflicts of interest in this work.

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