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Original Research Article

A prospective identification and mechanistic evaluation of clinically significant drug–drug interactions in chronic kidney disease patients using the Micromedex® database

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ABSTRACT

Background: Chronic kidney disease (CKD) patients are highly susceptible to drug–drug interactions (DDIs) due to polypharmacy and altered pharmacokinetics. To prospectively identify and characterize clinically significant DDIs in CKD patients using a standardized database approach.
Methods: A prospective observational study was conducted in 380 CKD patients (stages 1–5). Drug–drug interactions were identified using the Micromedex® database. Clinically significant DDIs were predefined as interactions classified as major or moderate severity or those requiring clinical intervention such as dose adjustment, monitoring, or drug avoidance. Interactions were categorized by severity and mechanism (pharmacokinetic/pharmacodynamic), including cytochrome P450 (CYP) involvement.
Results: A total of 61 clinically significant DDIs were identified, including 21 major, 28 moderate, and 12 minor interactions. Major DDIs were predominantly pharmacodynamic and associated with bleeding, nephrotoxicity, electrolyte imbalance, and cardiac conduction abnormalities. Pharmacokinetic interactions commonly involved CYP3A4, followed by CYP2D6, CYP2C9, and CYP2C19 enzymes.
Conclusion: Clinically significant DDIs are common in CKD patients and can be systematically identified using standardized tools such as Micromedex®. Most interactions are predictable and manageable through monitoring, dose adjustment, or avoidance strategies.

Keywords: Chronic kidney disease, Drug–drug interactions, Pharmacovigilance, Cytochrome P450, Polypharmacy

INTRODUCTION

Chronic kidney disease (CKD) represents a major global public health challenge, with a steadily increasing prevalence worldwide and a substantial contribution to cardiovascular morbidity, hospitalization, and premature mortality.[1-3] The rising burden of CKD is largely attributable to increasing rates of diabetes mellitus, hypertension, and population aging.

As kidney function declines, patients require long-term pharmacotherapy to manage associated comorbidities such as cardiovascular disease, anemia, and mineral and bone disorders.[4] The complexity of pharmacotherapy in CKD inevitably results in polypharmacy, which is a principal determinant of drug–drug interactions (DDIs).[5] Polypharmacy not only increases the likelihood of DDIs but also heightens the risk of adverse drug reactions, making safe prescribing a cornerstone of nephrology care.

Physiological changes accompanying CKD profoundly alter drug pharmacokinetics. Reduced glomerular filtration rate leads to impaired renal elimination of drugs and metabolites, while uremia alters plasma protein binding and drug distribution.[6] Beyond renal clearance, uremic toxins and chronic inflammation downregulate hepatic and

intestinal drug-metabolizing enzymes and transporters, particularly cytochrome P450 (CYP) isoenzymes.[7-9] Consequently, drugs primarily eliminated via hepatic pathways may exhibit altered pharmacokinetics in CKD.

Pharmacodynamic interactions are equally important. Drugs commonly prescribed in CKD—including diuretics, beta-blockers, calcium channel blockers, antiplatelet agents, anticoagulants, and immunosuppressants—often exert additive or synergistic effects on blood pressure, electrolyte balance, coagulation pathways, and cardiac conduction.[10,11] Such interactions may precipitate acute kidney injury, hyperkalemia, bleeding events, and arrhythmias, all of which are associated with poor prognosis in CKD patients.[12] Despite this recognized vulnerability, most available evidence is retrospective and lacks detailed mechanistic characterization.[13,14] Prospective pharmacovigilance studies are therefore essential to improve medication safety and guide rational prescribing in CKD.[15]

Despite the recognized risk of drug–drug interactions in CKD patients, there is limited prospective evidence using standardized and reproducible methods for identifying clinically significant DDIs. Many studies rely on retrospective data or lack mechanistic classification. Therefore, the present study aims to prospectively identify and mechanistically classify clinically significant DDIs in CKD patients using a standardized database (Micromedex®), with emphasis on severity grading and pharmacokinetic and pharmacodynamic mechanisms.

METHODS

Study design and setting

This prospective observational study was conducted at the Department of Nephrology, Muljibhai Patel Urological Hospital (MPUH), Nadiad, Gujarat, India, from September 2024 to January 2025. The study included adult patients (≥18 years) diagnosed with chronic kidney disease (stages 1–5) attending OPD, IPD, and dialysis units. A total sample size of 380 consecutive eligible patients was included based on availability during the defined study period (convenience sampling method). CKD staging was performed according to KDIGO guidelines. Estimated glomerular filtration rate (eGFR) was calculated using

Study population

Inclusion criteria

All gender patients, patients with comorbid conditions and all CKD patients above 18 years old were included.

Exclusion criteria

Pregnant and lactating women, the patient underwent renal transplantation and a patient admitted with acute kidney injury were excluded.

A total of 380 consecutive eligible CKD patients were included in the study.

Data collection

This observational study included 380 adults with CKD stages 1–5 attending a tertiary care hospital. Data were collected using a structured case record form. Demographic variables included age and sex. Clinical variables included CKD stage, age, gender, and current medication list.

Identification of drug–drug interactions

All prescribed medications were systematically screened for potential drug–drug interactions using the Micromedex® Drug Interaction Database. Each drug pair was independently evaluated to identify potential interactions. Duplicate interactions were excluded. Severity classification, mechanism (pharmacokinetic/ pharmacodynamic), and clinical effects were recorded based on the database evidence summaries.

Among all identified interactions, 61 DDIs were classified as clinically significant based on severity and potential to cause adverse clinical outcomes. These included 21 major, 28 moderate, and 12 minor interactions.

Definition of clinically significant DDIs

Associated with serious clinical outcomes, including bleeding, nephrotoxicity, electrolyte imbalance, or cardiac conduction abnormalities and required clinical intervention, such as dose adjustment, drug substitution, or enhanced monitoring

Classification of DDIs

Identified interactions were categorized based on severity (major, moderate, minor) and mechanism (pharmacokinetic or pharmacodynamic). Pharmacokinetic interactions were further evaluated for cytochrome P450 (CYP) enzyme and transporter involvement where applicable.

All identified DDIs were reproducible using the Micromedex® database criteria.

Ethical considerations

The study was submitted to the Muljibhai Patel Society for Research in Nephro-Urology Ethics Committee for Human Research for approval on 04 September 2024. The study was carried out to analyse prescription pattern and find out drug-drug interactions. The data was collected from the OPD, IPD, and dialysis unit. The main purpose of the study was well explained to the patients. Informed consent was maintained confidentially. After peer interviewing and reviewing, the study was approved by the ethics committee.

RESULTS

A total of 380 patients with CKD were included in the study. Using a standardized Micromedex® database screening approach and predefined criteria, 61 clinically significant drug–drug interactions were identified. All interactions were reproducible based on database classification.

As shown in Table 1, the study population (n=380) demonstrated a predominance of middle-aged and elderly patients. The largest proportion of patients belonged to the 41–60-year age group (44.7%), followed by those aged 61–80 years (30.5%). Younger adults aged 18–40 years accounted for 23.7%, while patients aged >80 years constituted only 1.1% of the cohort.

Table 1: Age-wise distribution of patients with chronic kidney disease (n=380).

Age group (years)	Number (N)	Percentage (%)
18–40	90	23.7
41–60	170	44.7
61–80	116	30.5
>80	4	1.1
Total	380	100

This distribution indicates that CKD and its associated pharmacotherapeutic complexity are most prevalent during middle and late adulthood, a period typically characterized by increasing comorbidities and medication burden, thereby predisposing patients to drug–drug interactions.

Demonstrates a clear male predominance, with 271 male patients (71.3%) compared to 109 female patients (28.7%). This gender imbalance may reflect higher prevalence of CKD-associated risk factors such as hypertension, diabetes mellitus, and cardiovascular disease among males in the studied population.

The predominance of male patients is clinically relevant, as sex-related differences in drug metabolism, body composition, and comorbidity patterns may further influence susceptibility to drug–drug interactions (Table 2).

The stage-wise distribution of CKD is presented in table 3. Advanced disease stages were highly prevalent, with stage 5 CKD accounting for 54.2% (n=206) of patients, followed by stage 4 CKD (19.2%, n=73). Early-stage CKD (stages 1 and 2 combined) constituted only 7.6% of the cohort. This skewed distribution toward advanced CKD reflects the tertiary care setting and underscores the complexity of pharmacotherapy in the study population. Advanced CKD is associated with reduced renal clearance, altered nonrenal drug metabolism, and a higher burden of comorbidities, all of which increase the likelihood of clinically significant DDIs.

Table 2: Gender distribution of the study population (n=380).

Gender	Number (N)	Percentage (%)
Male	271	71.3
Female	109	28.7
Total	380	100

Table 3: Distribution of patients according to CKD stage (KDIGO classification) (n=380).

CKD stage	Number (N)	Percentage (%)
Stage 1	8	2.1
Stage 2	21	5.5
Stage 3A	27	7.1
Stage 3B	45	11.8
Stage 4	73	19.2
Stage 5	206	54.2
Total	380	100

Table 4 summarizes the cytochrome P450 (CYP) enzymes implicated in the identified clinically significant DDIs. CYP3A4 was the most frequently involved enzyme, followed by CYP2D6, CYP2C9, and CYP2C19. A substantial number of interactions were classified as not enzyme-mediated, reflecting pharmacodynamic mechanisms or pharmacokinetic interactions related to drug binding or altered absorption.

The predominance of CYP3A4-mediated interactions is clinically important, as this enzyme is responsible for the metabolism of numerous cardiovascular drugs, immunosuppressants, and statins commonly prescribed in CKD. Altered CYP activity in CKD may further amplify the clinical impact of such interactions (Table 4).

Table 4: Distribution of CYP enzymes involved in clinically significant DDIs (n=61).

CYP enzyme/pathway	Number of interactions (N)
CYP3A4	17
CYP2D6	7
CYP2C9	6
CYP2C19	6
CYP2C8	4
OATP1B1	1
Not enzyme-mediated (PD binding/pH)	20
Total	61

Moderate DDIs constituted the largest proportion, followed by major interactions. More than one-third of interactions were classified as major, highlighting a substantial risk of serious adverse outcomes in the CKD population. These findings confirm that a substantial proportion of identified interactions were clinically relevant according to predefined severity criteria (Table 5).

Pharmacodynamic mechanisms predominated among clinically significant DDIs, indicating that additive or synergistic physiological effects play a major role in interaction-related harm in CKD. The predominance of pharmacodynamic interactions highlights the importance of additive physiological effects in CKD patients receiving multiple medications (Table 6). The identified DDIs were consistent with known pharmacological mechanisms and database evidence, supporting the validity of the identification approach (Table 7-9).

Table 5: Distribution of clinically significant drug–drug interactions by severity (n=61).

Severity of interaction	Number of interactions (N)	Percentage (%)
Major	21	34.4
Moderate	28	45.9
Minor	12	19.7
Total	61	100

Table 6: Mechanistic classification of clinically significant drug–drug interactions (n=61).

Mechanism of interaction	Number of interactions (N)	Percentage (%)
Pharmacodynamic (PD)	36	59
Pharmacokinetic (PK)	25	41
Total	61	100

Table 7: Major clinically significant drug–drug interactions in CKD (n=21).

No.	Drug pair	Severity	PK/ PD	CYP enzyme/ transporter	Interaction effect	Recommended alternative/ management
1	Aceclofenac – Dalteparin	Major	PD	Not enzyme-mediated	Major bleeding	Avoid NSAIDs, use paracetamol
2	Amlodipine – Clonidine	Major	PD	Not enzyme-mediated	Bradycardia, AV block	Avoid or close HR/BP monitoring
3	Amlodipine – Domperidone	Major	PD	CYP3A4 (domperidone)	QT prolongation	Use metoclopramide
4	Amlodipine – Tacrolimus	Major	PK	CYP3A4 inhibition	↑ Tacrolimus nephrotoxicity	Monitor trough levels
5	Aspirin – Clopidogrel	Major	PD	CYP2C19 (clopidogrel activation)	Bleeding	Risk–benefit assessment
6	Aspirin – Dalteparin	Major	PD	Not enzyme-mediated	Bleeding	Avoid combination
7	Aspirin – Furosemide	Major	PD	Not enzyme-mediated	Reduced diuresis, AKI	Use acetaminophen
8	Aspirin – Vancomycin	Major	PD	Not enzyme-mediated	Nephrotoxicity	Renal monitoring
9	Atenolol – Clonidine	Major	PD	Not enzyme-mediated	Bradycardia, rebound HTN	Taper clonidine
10	Atenolol – Diltiazem	Major	PD	CYP3A4 (diltiazem)	AV block	Use dihydropyridine CCB
11	Bisoprolol – Clonidine	Major	PD	CYP3A4 (bisoprolol)	Severe bradycardia	Monitor ECG
12	Cilostazol – Rivaroxaban	Major	PD	CYP3A4, CYP2C19	Major bleeding	Avoid combination
13	Ceftazidime – Furosemide	Major	PD	Not enzyme-mediated	Nephrotoxicity	Hydration + monitoring
14	Clonidine – Metoprolol	Major	PD	CYP2D6 (metoprolol)	AV block	Avoid combination
15	Dapagliflozin – Furosemide	Major	PD	Not enzyme-mediated	Volume depletion	Reduce diuretic dose
16	Furosemide – Metolazone	Major	PD	Not enzyme-mediated	Severe electrolyte loss	Monitor electrolytes

Continued.

No.	Drug pair	Severity	PK/ PD	CYP enzyme/ transporter	Interaction effect	Recommended alternative/ management
17	Mycophenolate – Sevelamer	Major	PK	Not CYP-mediated (binding)	↓ MPA absorption	Separate doses
18	Spironolactone – Tacrolimus	Major	PD	CYP3A4 (tacrolimus)	Hyperkalemia	Avoid combination
19	Atorvastatin – Cyclosporine	Major	PK	CYP3A4, OATP1B1	Rhabdomyolysis	Use pravastatin
20	Ciprofloxacin – Tacrolimus	Major	PK	CYP3A4 inhibition	↑ Tacrolimus + QT	Monitor levels
21	Nifedipine – Tacrolimus	Major	PK	CYP3A4	Tacrolimus toxicity	Dose adjustment

Table 8: Moderate clinically significant drug–drug interactions in CKD (n=28).

No.	Drug pair	Severity	PK/ PD	CYP enzyme/ transporter	Interaction effect	Management
1	Amlodipine – Diltiazem	Moderate	PK	CYP3A4 inhibition	↑ Amlodipine levels	BP monitoring
2	Amlodipine – Ciprofloxacin	Moderate	PK	CYP3A4 inhibition	Hypotension	Dose adjustment
3	Aspirin – Atenolol	Moderate	PD	Not enzyme-mediated	↓ BP control	Monitor BP
4	Aspirin – Bisoprolol	Moderate	PD	CYP3A4 (bisoprolol)	Reduced antihypertensive effect	Monitor BP
5	Aspirin – Sodium Bicarbonate	Moderate	PK	Not CYP-mediated	↓ Aspirin absorption	Separate dosing
6	Atorvastatin – Clopidogrel	Moderate	PK	CYP3A4, CYP2C19	↓ Antiplatelet effect	Switch statin
7	Bisoprolol – Diclofenac	Moderate	PD	CYP2C9 (diclofenac)	Renal/BP compromise	Avoid NSAIDs
8	Calcium – Metolazone	Moderate	PD	Not enzyme-mediated	Hypercalcemia	Monitor Ca^{2+}
9	Carvedilol – Prazosin	Moderate	PD	CYP2D6, CYP2C9	First-dose hypotension	Start low
10	Clonidine – Levocetirizine	Moderate	PD	Not enzyme-mediated	Sedation	Avoid CNS depressants
11	Clopidogrel – Torsemide	Moderate	PK	CYP2C19	↑ Torsemide toxicity	Clinical monitoring
12	Dapagliflozin – Levothyroxine	Moderate	PD	Not enzyme-mediated	Glycemic fluctuation	Monitor glucose
13	Furosemide – Sucralfate	Moderate	PK	Not enzyme-mediated	↓ Diuretic effect	Separate doses
14	Glimepiride – Linagliptin	Moderate	PD	CYP2C9 (glimepiride)	Hypoglycemia	Dose reduction
15	Iron – Mycophenolate	Moderate	PK	Not CYP-mediated	↓ MPA exposure	Separate doses
16	Levothyroxine – Sevelamer	Moderate	PK	Not CYP-mediated	Hypothyroidism	TSH monitoring
17	Levothyroxine – Sodium Bicarbonate	Moderate	PK	Not CYP-mediated	↓ Absorption	Dose spacing

Continued.

No.	Drug pair	Severity	PK/ PD	CYP enzyme/ transporter	Interaction effect	Management
18	Linagliptin – Metoprolol	Moderate	PD	CYP2D6	Masked hypoglycemia	Patient education
19	Linagliptin – Repaglinide	Moderate	PK	CYP3A4, CYP2C8	Hypoglycemia	Dose adjust
20	Metformin – Prednisolone	Moderate	PD	CYP3A4 (prednisolone)	Hyperglycemia	Glucose monitoring
21	Nebivolol – Prazosin	Moderate	PD	CYP2D6	Excess hypotension	BP monitoring
22	Repaglinide – Rifampin	Moderate	PK	CYP3A4 and CYP2C8 induction	Loss of efficacy	Avoid
23	Sodium Bicarbonate – Aspirin	Moderate	PK	Not CYP-mediated	↓ Aspirin effect	Dose separation
24	Tacrolimus – Valganciclovir	Moderate	PD	CYP3A4	Nephrotoxicity	Renal monitoring
25	Glipizide – Nebivolol	Moderate	PD	CYP2C9, CYP2D6	Masked hypoglycemia	Monitor glucose
26	Atenolol – Linagliptin	Moderate	PD	Not enzyme-mediated	Glycemic alteration	Monitor glucose
27	Metoprolol – Metformin	Moderate	PD	CYP2D6	Masked hypoglycemia	Educate patient
28	Carvedilol – Repaglinide	Moderate	PK	CYP2C8, CYP3A4	Hypoglycemia	Dose adjust

Table 9: Minor clinically significant drug–drug interactions in CKD (n=12).

No.	Drug pair	Severity	PK/ PD	CYP enzyme	Effect	Management
1	Ferric carboxy-maltose – Sodium bicarbonate	Minor	PK	Not enzyme-mediated	↓ Iron absorption	Monitor
2	Ferrous fumarate – Sodium bicarbonate	Minor	PK	Not enzyme-mediated	↓ Iron bioavailability	Separate doses
3	Sodium bicarbonate – Sucroferric oxyhydroxide	Minor	PK	Not enzyme-mediated	↓ Iron efficacy	Routine care
4	Calcium/Magnesium – Iron sucrose	Minor	PK	Not enzyme-mediated	↓ Iron absorption	Dose spacing
5	Calcium carbonate – Aspirin	Minor	PK	Not enzyme-mediated	↓ Aspirin absorption	Separate dosing
6	Calcium acetate – Aspirin	Minor	PK	Not enzyme-mediated	↓ Salicylate effect	Separate doses
7	Iron – Pantoprazole	Minor	PK	CYP2C19 (pantoprazole)	↓ Iron absorption	Monitor ferritin
8	Ferrous fumarate – Pantoprazole	Minor	PK	CYP2C19	↓ Iron bioavailability	Consider IV iron
9	Ferric carboxymaltose – Antacids	Minor	PK	Not enzyme-mediated	↓ Iron efficacy	Monitoring
10	Sodium bicarbonate – Levothyroxine	Minor	PK	Not enzyme-mediated	↓ Thyroxine absorption	Dose spacing
11	Iron – Antacids	Minor	PK	Not enzyme-mediated	↓ Iron absorption	Separate doses
12	Ferrous salts – Calcium products	Minor	PK	Not enzyme-mediated	↓ Iron absorption	Administer separately

DISCUSSION

This prospective observational study identified a substantial burden of clinically significant DDIs among patients with chronic kidney disease using a standardized Micromedex® database approach. The findings demonstrate that DDIs in CKD are common and can be systematically identified and categorized based on severity and mechanism. These findings are consistent with known pharmacological mechanisms and previously reported patterns in CKD populations.[1-3] Major DDIs were predominantly pharmacodynamic and involved drug classes commonly prescribed in CKD, including antiplatelet agents, anticoagulants, diuretics, cardiovascular drugs, and immunosuppressants. These interactions were associated with serious outcomes such as bleeding, nephrotoxicity, electrolyte disturbances, and cardiac conduction abnormalities, consistent with previous CKD studies.[5,12]

Moderate DDIs exhibited heterogeneous mechanisms and clinical impact, often requiring dose adjustment or enhanced monitoring. Minor DDIs were largely pharmacokinetic and primarily affected drug absorption, particularly involving iron preparations, calcium salts, antacids, and thyroid medications.[10,11]

A major strength of this study is the mechanistic differentiation between pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic DDIs frequently involved CYP3A4, CYP2C9, CYP2D6, and CYP2C19. Altered CYP activity in CKD, driven by uremic toxins and inflammation, may amplify the clinical significance of these interactions even at standard doses. Pharmacodynamic interactions predominated in this study, reflecting the additive or synergistic effects of commonly co-prescribed drugs in CKD patients. Pharmacokinetic interactions were primarily mediated through CYP enzymes, particularly CYP3A4, highlighting the role of altered drug metabolism in this population.[7-9,11]

The identified DDIs were largely predictable and manageable through appropriate clinical strategies such as dose adjustment, drug substitution, and monitoring. These findings emphasize the importance of structured medication review using electronic databases in routine clinical practice.[14,17]

A key strength of this study is the use of a standardized and reproducible database (Micromedex®) for DDI identification, along with mechanistic classification and severity grading.

Limitations

This study has certain limitations. It was conducted at a single center, which may limit generalizability. Additionally, DDIs were identified based on database evidence rather than direct clinical outcome assessment. Future studies incorporating clinical endpoints are warranted.

CONCLUSION

Clinically significant drug–drug interactions are common in patients with chronic kidney disease and can be systematically identified using standardized tools such as the Micromedex® database. The majority of interactions are predictable and primarily pharmacodynamic in nature. These interactions can be effectively managed through appropriate strategies, including monitoring, dose adjustment, and avoidance of high-risk combinations. Incorporating structured DDI screening into routine clinical practice may enhance medication safety in this high-risk population.

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

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