Original Article

Prevalence and Pattern of Potential Drug-Drug Interactions among Chronic Kidney Disease Patients in South-Western Nigeria

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Abstract

Background: Management of chronic kidney disease (CKD) patients often requires the use of multiple drugs due to a high number of cardiovascular risk factors and complications associated with the disease. Multiple drugs predispose to potential drug-drug interactions (DDIs) which may be associated with increased morbidity, mortality, length of hospital stay and health-care cost. **Objectives:** This study determined the prevalence and pattern of potential DDIs among CKD patients attending Kidney Care Centre, in Ondo City, Nigeria. **Methodology:** It was an 18-month retrospective study that involved the reviewed CKD patients' records. The Lexi-Interact database was used to evaluate patients' medications for potential DDIs. **Results:** One hundred and twenty-three (123) CKD patients, made up of 82 (66.67%) males and 41 (33.33%) females were studied. The mean age of the CKD patients was 53.81 ± 16.03 years. The most common comorbid conditions were hypertension in 103 (83.74%) and diabetes mellitus in 39 (31.71%). A total of 1237 prescriptions were made and the mean number of prescribed medications per patient was 10.06 ± 3.97. A total number of 1851 potential DDIs were observed among 118 patients. The prevalence of potential DDIs was 95.9% while the mean DDIs per prescription was 1.27. Among the potential DDIs observed, the severity was mild in 639 (34.5%), moderate in 1160 (62.7%), major in 51 (2.8%) and only 1 (0.1%) was of avoid drug combination. The most frequent DDI was between calcium carbonate and oral ferrous sulphate. **Conclusion:** The prevalence of potential DDIs is high among CKD patients. About 63% of these interactions have moderate severity. Clinicians and pharmacists should utilise available DDI software to avoid harmful DDIs in CKD patients.

Keywords: Chronic kidney disease, drug-drug interactions, pattern, potential, prevalence

Introduction

Chronic kidney disease (CKD) is a major public health problem due to its increasing incidence, prevalence and associated economic burden. The global prevalence of CKD is estimated to be 11%–13%.[1] The prevalence of CKD in Nigeria varies between 6% and 12% from both community and hospital-based studies.[2-5] Cardiovascular disease burden in CKD is high and associated with increased hospitalisation rate, morbidity and mortality.[6-8]

Cardiovascular risk factors such as hypertension, diabetes mellitus, anaemia, calcium-phosphate abnormalities, hyperuricemia and left ventricular hypertrophy are highly prevalent in CKD patients.[9,10] These contribute to the burden of cardiovascular disease and complications in CKD patients. The proper management of cardiovascular disease and its risk factors is important in retarding the progression of CKD and reducing mortality.[7,9] This tend to involve the use of several medications in the management of CKD patients such that polypharmacy is often practiced. The consequences of polypharmacy include poor patients' medication compliance due to high pill burden, increased cost of care and most importantly drug-drug interactions (DDIs) which may have deleterious effects.

DDI can be defined as an appreciably harmful or beneficial process whereby the pharmacologic effect of a drug is directly

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or indirectly influenced and modified by the presence of another drug which can result in either treatment failure (antagonistic interaction) or drug-induced toxicity (synergistic/additive interaction).[11] It may result from a number of processes which is either related to the pharmacokinetic or pharmacodynamic properties of the drugs. Consequences of DDIs include increase or decrease in efficacy of treatment and adverse drug reactions.

DDIs constitute a major clinical problem, accounting for 2%–6% of all hospital admissions with an estimated annual cost to the National Health Service of about ≤500 million in the United Kingdom.[12] In a meta-analysis of 39 prospective studies from hospitals in the United States, it was shown that DDIs ranked fourth to sixth as a leading cause of death.[13] Al-Hajje *et al*. also reported that DDI was the most common drug-related problem in hospitalised medical patients in University Hospital of Beirut.[14]

The prevalence of potential DDIs in CKD patients from previous reports ranged between 59.1% and 89.1%.[15-20] This relatively high prevalence is due to the polypharmacy involved in the management of this condition. It is associated with increased morbidity, mortality, length of hospital stay and health-care cost.[21-25] The added burden of harmful DDIs and its consequences in CKD patients are preventable because of their predictable nature. Various software are available that can detect potential DDIs and include British National Formulary, Drug Interaction Facts, Medscape, Epocrates, Lexi-Interact, Harmavista and Stockley's drug interactions.

This study determined the prevalence and pattern of potential DDIs among CKD patients attending a kidney hospital in Southwest, Nigeria. The goal was to increase awareness of the burden of potential DDIs in renal medicine and emphasise the need to regularly evaluate prescriptions for drug-related problems.

Methodology

This study was a descriptive retrospective study carried out at Kidney Care Centre, Ondo City. This tertiary health institution is located in Southwest Nigeria and receives a referral from within and outside Ondo State.

The case records of 123 adult patients with CKD who were managed at the centre over 18-month between January 2015 and June 2016 were reviewed for the study. The following information was extracted: sociodemographic data, serum creatinine, number and list of medications at the time of last clinic attendance for outpatients and at the time of discharge for those that received in-patient care and comorbidities such as hypertension, diabetes mellitus, HIV infection, stroke and heart failure.

The serum creatinine was used to calculate the estimated glomerular filtration rate (eGFR) using Chronic Kidney Disease Epidemiology Collaboration (CKP-EPI) formula and CKD staging was done using eGFR as follows: stage 1 (glomerular filtration rate [GFR] of ≥90 ml/min with evidence of kidney damage), Stage 2 (GFR of 60–89 ml/min with evidence of kidney damage), Stage 3 (GFR of 59–30 ml/min with or without evidence of kidney damage), Stage 4 (GFR of 15–29 ml/min with or without evidence of kidney damage) and Stage 5 (GFR <15 ml/min with or without evidence of kidney damage).[26]

The Lexi-Interact database was used to evaluate patients' medication regimen for potential DDIs. Lexi-Interact database has been reported to show the best results in precision analysis.[27] The Lexi-Interact database system provides accurate information about the risk, type, mechanism and pattern of distribution of potential DDIs. It also gives recommendation (s) on how to prevent and manage DDIs if they occur. The software identifies and classifies DDIs into five types according to the degree of clinical significance. Type A: No known interaction, Type B: Minor or mild interaction, Type C: Moderate or significant interaction, Type D: Major or serious interaction and Type X: contraindication or avoid combination.

Ethical Approval was obtained from Health Research Ethics Committee of State Specialist Hospital, Akure, Ondo State on the August 20, 2016 (Reference Number: AA2/Neph/200816).

Data analysis

Data generated were analysed using the SPSS version 21.0 by IBM (Armonk, New York, USA). Results were presented in tabular form. Discrete variables were presented as frequency and percentages. Continuous variables were presented as means and standard deviation.

Results

A total of 123 CKD patients made up of 82 (66.67%) males and 41 (33.33%) females were studied. The mean age of study patients was 53.81 ± 16.03 years. Forty-eight (39.0%) were between 18 and 49 years, 52 (42.3%) were between 50 and 69 years and the remaining 23 (18.7%) were 70 years and above [Table 1].

Fifty-three (43.09%) of study individuals had tertiary education, 36 (29.3%) had secondary education, 18 (14.6%) had a primary education while 16 (13.0%) had no formal education. Eighty-six (69.9%) of the study individuals were in CKD Stage 5, 15 (12.2%) were in CKD Stage 4 and 19 (15.5%) were in CKD Stage 3. Two (1.6%) in CKD Stage 2 and the remaining one in CKD Stage 1 [Table 1].

The most common comorbid conditions were hypertension in 103 (83.74%) and diabetes mellitus in 39 (31.71%), with heart failure in 11 (8.9%), HIV in 7 (5.7%) and stroke in 5 (4.1%) [Table 1].

A total number of 1237 medications were prescribed for the study individuals, and the mean number of prescribed medications per patient was 10.06 ± 3.97. Eighteen CKD individuals (14.6%) were on ≤5, 43 (35.0%) were on 6–10 medications, 51 (41.5%) were on 11–15 medications and 11 (8.9%) were on ≥16 medications [Table 1].

The most frequently prescribed medications were furosemide 88 (71.6%), lisinopril 65 (52.9%), oral calcium carbonate

63 (51.2%), α-calcidol 62 (50.4%), erythropoietin 61 (49.6%) intravenous iron sucrose 60 (48.8%), amlodipine 56 (45.5%), hydrochlorothiazide 53 (43.1%), folic acid 53 (43.1%) and ferrous sulphate 50 (40.7%) [Table 2].

A total number of 1851 potential DDIs were identified among 118 individuals (95.9%) while five individuals (4.07%) had no known DDI. The prevalence of potential DDIs was 95.9%. Twenty-nine (23.6%) had between 6 and 10 interactions, 26 (21.1%) had 11–15 interactions while 16 (13.0%) had between 21 and 25 interactions [Table 3].

The range for the number of potential interactions among the 118 patients was from 1 to 85 interactions with a mean value of 15.69 ± 11.00 interactions. The most common pattern of DDI was between calcium carbonate and ferrous sulphate in 155 (8.4%) [Table 4].

A total of 639 (34.5%) interactions were of mild severity (Type B), 1160 (62.7%) were of moderate severity (Type C), 51 (2.8%) were of major severity (Type D) and only 1 (0.1%) was of avoid drug combination (Type X) [Table 5]. A total of 960 (52%) DDIs were pharmacokinetic interaction while the remaining (891) 48% were pharmacodynamic interactions.

Discussion

The prevalence of potential DDIs in this study was 95.9% which is higher than 59.1%–89.1% reported in some previous studies.[15-20] However, the reported prevalence in this study is higher than 59.1% reported by Sgnaolin *et al*.[15] Differences in methodology, average number of medications per prescription and stage of CKD of the studied population could account for variation in the prevalence rates of potential DDIs in the studies. An example is a study by Sgnaolin *et al*.[15] where a lower prevalence of potential DDIs was reported compared to this study, the average number of medication per prescription was 6.3 ± 3.1, unlike this present study where the average number of medication per prescription was 10.06 ± 3.97. The number of medications per prescription has been noted in some studies as one of the major determinants of potential DDIs.[15,18,20]

The mean prescribed drug in this study per patient was 10.06 ± 3.97. This is slightly higher than 7.87 ± 2.44 reported by Al-Ramahi *et al*.[17] However, Rama *et al*. reported a higher mean prescribed drugs per patients of 12.08 ± 6.30 compared to the finding in this present study.[16] Our study population involved both predialysis and dialysing patients unlike the study by Al-Ramahi *et al*. that involved only CKD patients on maintenance haemodialysis (MHD). Patients who are on regular MHD may require less number of drugs for blood pressure control. This may possibly explain the lower mean number of prescribed medications. The practice of polypharmacy in the management of CKD is necessary because of cardiovascular risk factors, comorbidities and complications which include hypertension, diabetes mellitus, heart failure, arrhythmias, anaemia, hyperuricemia and calcium-phosphate abnormalities that merit combination of drugs.

Table 1: Characteristics of study population

Characteristics	Frequency (%)/mean±SD
Gender	
Male	82 (66.7)
Female	41 (33.3)
Mean age (years)	53.81±16.03
Age group (years)	
20-49	48 (39.0)
50-69	52 (42.3)
≥70	23 (18.7)
Level of education	
No formal education	16 (13.0)
Primary	18 (14.6)
Secondary	36 (29.3)
Tertiary	53 (43.1)
CKD stage	
1	1 (0.8)
2	2 (1.6)
3	19 (15.5)
4	15 (12.2)
5	86 (69.9)
Co-morbidities	
Hypertension	103 (83.7)
Diabetes mellitus	39 (31.7)
HIV	7 (5.7)
Heart failure	11 (8.9)
Stroke	5 (4.1)
Mean prescribed medication per patient	10.06±3.97
Number of prescribed medications	
≤5	18 (14.6)
6-10	43 (35.0)
11-15	51 (41.5)
≥16	11 (8.9)

CKD: Chronic kidney disease, SD: Standard deviation

Table 2: Most frequently prescribed medications

Medication	Frequency (%)
Furosemide	88 (71.6)
Lisinopril	65 (52.9)
Calcium carbonate	63 (51.22)
Alphacalcidol	62 (50.4)
Erythropoieitin	61 (49.6)
Intravenous iron	60 (48.8)
Amlodipine	56 (45.5)
HCTZ	53 (43.1)
Folic acid	53 (43.1)
OFS	50 (40.7)
Astyfer	47 (38.2)
Vitamin C	40 (32.5)
Alpha-methyldopa	32 (26.0)
Atorvastatin	30 (24.4)
Insulin	25 (20.3)
Valsartan	24 (19.5)

HCTZ: Hydrochlorothiazide, OFS: Oral ferrous sulphate

The most common comorbidities in this study were hypertension and diabetes which agrees with previous reports.[19,20,28] This may be due to the fact that both conditions are the leading aetiologies of CKD worldwide.

The average number of DDIs per prescription in this study was 1.27 which is similar to the report by Sgnaolin *et al*.[15] but lower than the figure reported by Rama *et al*. and Marquito *et al*.[16,19] This, therefore, underscores the need for physicians and clinical pharmacists to regularly evaluate prescriptions for CKD patients for DDI.

The most commonly prescribed drugs in this study were furosemide, lisinopril and calcium carbonate. This agrees with previous studies where calcium carbonate and furosemide were among the most frequently prescribed medications.[17,19]

The most common potential DDI in this study was between oral calcium carbonate and oral ferrous sulphate. The intestinal absorption of oral iron may be reduced when administered with calcium carbonate because of the effect of the latter in increasing the gastrointestinal pH. This is similar to findings from studies by Hedge *et al*. and Sgnaolin *et al*.[15,20] They reported interactions between calcium carbonate and ferrous sulphate as among the most frequent DDIs in their studies.[15,20] However, Rama *et al*. reported DDI between ascorbic acid and cyanocobalamin while Al-Ramahi *et al*. reported DDI between calcium carbonate and amlodipine as the most frequent DDIs in their respective studies.[16,17]

Table 3: Potential drug-drug interactions in study population

Number of DDIs	Frequency (%)
None	5 (4.1)
1-5	15 (12.2)
6-10	29 (23.6)
11-15	26 (21.1)
16-20	15 (12.2)
21-25	16 (13.0)
≥26	17 (13.8)

DDIs: Drug-drug interactions

Regarding the degree of clinically significant interactions, about 63% of the interactions were of moderate severity (Type C) which is similar to previous reports.[15,16,19,20] In this study, the prevalence of Type X interaction (avoid drug combination) was 0.1% which was only found in one subject. This is comparable to 0.4% reported by Marquito *et al*.[19] This finding is however at variance to that of Saleem *et al*. who reported 13.4% of potential DDIs as avoid drug combination.[18] The only Type X interaction in this study occurred between intravenous calcium gluconate and intravenous ceftriaxone which carries the potential risk of fatal particulate precipitation and deposition in the lungs and kidneys. The administration interval between ceftriaxone and any calcium containing solution such as Ringer's solution, Hartman solution or intravenous calcium gluconate must be separated by at least 48 h.

A slightly higher proportion (52%) of potential DDIs was found to be from pharmacokinetic interactions. This is different from reports from other studies where pharmacodynamic interaction was found to be predominant.[16,20] Furthermore, the majority of the potential DDIs were of delayed onset similar to the report by Rama *et al*.[16] The clinical significance of this is that patients may not manifest the effects of DDI early, hence the need for long-term follow-up of such patients.

The clinical pharmacists also have major role to play in preventing DDI by evaluating physicians' prescriptions for possible DDI.[14,29] Therefore, integrated professional interaction should be encouraged between nephrologist/physicians and clinical pharmacists to optimise CKD patients' care. Vigilance by health workers such as clinicians, pharmacists and nurses in detecting, diagnosing and reporting drug interactions particularly in at-risk patients such CKD patients is also vital for continued drug safety monitoring.

Table 4: Pattern of common specific drug-drug interactions and their potential adverse effects

Pattern of specific drug interactions	*n* (%)	Mechanism of interaction	Potential adverse effects
$CaCO_3$ + OFS	155 (8.37)	Pharmacokinetic, Type B and C	$CaCO_3$ will decreases intestinal absorption of OFS by increasing GIT pH and vice-versa
Folic acid + furosemide	63 (3.40)	Pharmacokinetic, Type B	Furosemide increases renal clearance of folic acid
α-Calcidol + $CaCO_3$	60 (3.24)	Pharmacokinetic, Type C	Hypercalcaemia
OFS + Vitamin E	56 (3.03)	Pharmacokinetic, Type C	Vitamin E decreases GIT absorption of OFS
$CaCO_3$ + furosemide	49 (2.65)	Pharmacokinetic, Type B	Furosemide increases renal clearance of calcium
Furosemide + lisinopril	49 (2.65)	Pharmacodynamics, Type C	Acute hypotension and renal insufficiency
Furosemide + HCTZ	42 (2.27)	Pharmacodynamics, Type C	Hypokalaemia
Folic acid + HCTZ	35 (1.89)	Pharmacokinetic, Type B	HCTZ increases renal clearance of folic acid
Heparin + Vitamin E	35 (1.89)	Pharmacodynamics, Type B	Increase risk of bleeding/haemorrhage due to their anticoagulant effect
Heparin + lisinopril	34 (1.84)	Pharmacodynamics, Type C	Low molecular weight heparin may suppresses adrenocortical aldosterone secretion thereby leading to hyperkalaemia
Amlodipine + $CaCO_3$	32 (1.73)	Pharmacodynamics, Type C	$CaCO_3$ antagonises and decreases the vasodilatory effect of amlodipine on the small arteries thereby reducing the antihypertensive effect

OFS: Oral ferrous sulphate, HCTZ: Hydrochlorothiazide, GIT: Gastrointestinal

Table 5: Severity of drug-drug interactions

Severity of DDIs	Frequency (%)
Type B (mild severity)	639 (34.5)
Type C (moderate severity)	1160 (62.7)
Type D (major severity)	51 (2.7)
Type X (avoid drug combination)	1 (0.1)

DDIs: Drug-drug interactions

The limitation of this study is that potential DDIs detected were theoretical and may not occur in clinical settings. In addition, the Lexi-Interaction checker used in this study did not take into consideration the prescribed dose, frequency of administration, route of administration and duration of medication. However, our study has brought to the limelight the magnitude of potential DDIs among CKD patients and the need to take proactive steps to reduce the additional burden on CKD patients.

Conclusion

The prevalence of potential DDIs is high among CKD patients. Most of these interactions have moderate severity and delayed onset, hence the need to follow these patients up after drug prescription to reduce associated morbidity and mortality.

Recommendation

Physicians and pharmacists should make use of available interaction softwares to check all prescribed medications for the presence of potentially significant interactions. Regular interaction should be encouraged between nephrologist/physicians and clinical pharmacists in order to optimise CKD patients' care and reduce the occurrence of harmful drug interactions.

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Conflicts of interest

There are no conflicts of interest.

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