ORIGINAL ARTICLE

Evaluation of Drug-Drug Interactions Among Chronic Kidney Disease Patients of Nephrology Unit in the University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu State

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ABSTRACT

Context: Chronic kidney disease (CKD) patients are at high risk of drug-drug interactions (DDIs) that may require dose adjustments or the avoidance of drug combinations. **Aim:** To evaluate DDIs among chronic kidney disease patients of nephrology unit in the University of Nigeria Teaching Hospital (UNTH), Enugu in South-East Nigeria. **Settings and Design:** This study was a retrospective review of CKD patients who received treatment at the nephrology unit of UNTH between January 2004 and December 2014. **Methods and Materials:** The drug-drug interactions (DDIs) of the prescribed drugs were classified using the Medscape drug interaction checker. **Statistical Analysis used** the data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc, Version 16.0, Chicago, USA). The predictors of the DDIs were explored through linear regression with number of DDIs as the dependent variable. **Results:** A total of 898 DDIs were identified from the folders of the 169 CKD patients that were eligible. Majority were above 50 years old and in renal disease stage 4 or 5. Furosemide, lisinopril and amlodipine were the most frequently prescribed drugs and had the greatest likelihood for nephrotoxicity. The number of medications and hypertension (as co-morbidity) were the independent predictors of DDIs among the patients. Majority of the DDIs (64.14%) were significant. The most common interactions were between lisinopril and furosemide; furosemide and calcium carbonate; lisinopril and calcium carbonate. **Conclusion:** The prevalence of significant DDIs was high among the renal patients. The major determinants of the DDIs were the number of medications and the presence of hypertension as co-morbidity.

Key words: Drug-drug interactions, chronic kidney disease, medscape drug interaction checker, UNTH

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Key Message

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INTRODUCTION

Renal function should be considered before prescriptions are made.[1] About half of all drugs and their metabolites are excreted by the kidneys and more than a fifth of all adverse effects of medications have either a renal cause or renal effect.[2] However, pharmacists and other health professionals, need to be aware that not all drugs depend on the renal function. Renal impairment may cause toxicity due to the accumulation of medicines, especially if the medicine has a narrow safety margin.[1] Renal function monitoring is recommended for patients using medicines that are nephrotoxic.[1]

Drug therapy problems may arise in the use of medicines in renally-impaired patients. A drug therapy problem (DTP) is an event or circumstance that involves drug therapy and actually or potentially interferes with desired health outcomes.[3] Thus, the occurrence of a DTP could prevent or delay patients from achieving desired therapeutic goals.[4] An actual DTP is an event that has already occurred in a patient, whereas a potential DTP is an event that is likely to develop if pharmacists do not make any appropriate interventions. Prominent drug-related problems are adverse reactions, drug interactions and therapeutic failure.[5]

Chronic Kidney Disease (CKD) refers to kidney damage, manifested by abnormal excretion of albumin or reduced kidney function, quantified by measured or estimated glomerular filtration rate (GFR) persisting for greater than three months.[6,7] Individuals with CKD often require different classes of drugs placing them at risk for the development of drug interactions.[8,9] Drug interactions may increase morbidity, lead to hospitalizations and deaths.[10]

A Medscape drug interaction checker, a drug interaction tool, checks interacting drug ingredients, their effects and clinical significance. The drug-drug interactions (DDIs) are classified as serious, significant or minor. Serious DDIs require an alternative drug; significant DDIs require close monitoring while minor DDIs are non-significant DDIs.[11]

It is hoped that this study will help raise awareness on the relevant DDIs that occur among CKD patients and help health professionals have a better understanding on the topic in terms of prevalence and causes making it possible for such interactions to be avoided, if necessary. The general objective of the study was to evaluate drug-drug interactions in chronic kidney disease patients in the University of Nigeria Teaching Hospital, Enugu, South-East Nigeria. The specific objectives were: (i) To assess drug-drug interactions based on the Medscape classification (ii) To determine the number of drugs accounting for 90% of drug use (iii) To predict the causes of drug-drug interaction (iv) To assess the prescribed drugs that affect serum potassium level (v) To determine the prescribed drugs that are nephrotoxic.

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SUBJECTS AND METHODS

The study was a ten-year retrospective review of chronic kidney disease patients who received treatment at the nephrology unit of University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla, Enugu State between January 2004 and December 2014. Ethical approval was obtained from the Health Research and Ethics Board of UNTH prior to commencement. The University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla is located about 20 kilometers from Enugu Capital City along Enugu-Port Harcourt Express Way. This tertiary institution is a federal referral hospital that has numerous specialty units that serve patients mainly from the Eastern part of Nigeria. The study participants were renal disease patients who fulfilled the inclusion criteria and had no exclusion criteria. The inclusion criteria were patients diagnosed of renal disease with known serum creatinine levels. The exclusion criteria included patients with glomerular filtration rate greater than 90 ml/min/1.73 m^2 and those who were pregnant.

A total of 169 eligible renal disease patients folders were included and utilized in this study. A data collection form was developed using other research works on drug therapy problems, especially the University of Michigan Health System (UMHS) Chronic Kidney Disease Guidelines, March 2014.[12] Documentation included data on patient characteristics (e.g., age, gender); clinical characteristics such as the presence of comorbidities; renal disease stage; concurrent medications; drugs that increase serum potassium levels; drugs that decrease serum potassium levels and nephrotoxic drugs. The drug-drug interactions of the prescribed drugs were classified using the Medscape drug interaction checker. In the drug interactions per prescription, any interaction that occurred be it minor, significant or serious was recorded as one.

The data were collated and analyzed using the Statistical Package for Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc, Version 16.0, Chicago, USA). Descriptive statistics were used to summarize data. The linear regression was used to determine the independent predictors of drug-drug interactions. P –value ≤ 0.05 was considered statistically significant.

RESULTS

Most of the patients were female (52.1%) with about 54.4% above 50 years old. More than half of the patients (56.2%) were in renal disease stage 4 or 5 [Table 1]. The prescribed drugs that made up 90% utilization in patients prescriptions included the antihypertensive drugs: furosemide, lisinopril and amlodipine [Table 2]. The number of medications was an independent predictor of drug-drug interaction in model 1 while number of medications and hypertension as co-morbidity were the independent predictors of drug-drug interaction in model 2 of the linear regression. It indicated that for every additional one medication there would be an additional one DDI occurring and for the presence of hypertension as co-morbidity with/without any other co-morbidity there would be an additional 1.5 DDIs occurring provided other variables were constant [Table 3]. The clinical classification (serious, significant and minor) of the drug-drug interactions was presented in Table 4, while interacting drugs were presented in Table 5. A total of 898 drug-drug interactions were identified in the prescriptions of 169 patient's folders that were assessed. Majority of the drug-drug interactions (64.14%) were significant [Table 4]. The most common interactions were between lisinopril and furosemide; furosemide and calcium carbonate; lisinopril and calcium carbonate [Table 5]. Lisinopril and furosemide were the most frequently prescribed drugs that could increase and decrease serum potassium levels respectively [Table 6] while furosemide, lisinopril and amlodipine were the most frequently prescribed drugs that were nephrotoxic [Table 7].

DISCUSSION

More than half of the renal patients were female, above 50 years old and in renal disease stage 4 or 5. Furosemide, lisinopril and amlodipine were the most utilized drugs. The number of medications and hypertension, as co-morbidity, were the major predictors of drug-drug interactions. For every additional one medication there would be one additional DDI and for the presence of hypertension as co-morbidity with/without any other co-morbidity there would be additional 1.5 drug-drug interaction. Majority of the drug-drug interactions were significant. The most common interactions were between lisinopril and furosemide; furosemide and calcium carbonate; lisinopril and calcium carbonate. Lisinopril and furosemide were the most frequently prescribed drugs that could increase and decrease serum potassium levels, respectively. Furosemide, lisinopril and amlodipine were the most frequently prescribed drugs that were nephrotoxic. In this study, the mean age of patients with renal disease was approximately 51 years and this supports the research works that pointed out older age as a risk factor for the occurrence of polypharmacy and the development of chronic kidney disease.[1,13] In a study among CKD patients in a tertiary care hospital in India, most of the recorded DDIs occurred in patients between 51-70 years.[13] On average, there is a decline in the glomerular filtration rate by about 10 mL/min every 10 years after the age of 40.[1]

Not much difference was observed in the number of male patients having CKD when compared to that of the female patients. The females were slightly more than the males at a ratio of 52.1:47.9. This was similar to a study on the prevalence of potentially inappropriate medication prescribing in elderly patients with CKD which had a female predominance.[14]

Hypertension was also found to be the highest occurring co-morbidity and patients with hypertension as a co-morbid state had higher risk of drug-drug interactions. Anti-hypertensive have been indicated with a high number of DDIs.[10,13] The number of prevalent CKD patients will continue to rise, reflecting the growing elderly population and increasing numbers of patients with diabetes

Table 1: Patient Characteristics

Characteristics	n (%)
Age	
≤ 18	2 (1.2)
19-35	25 (14.8)
36-50	50 (29.6)
51-65	68 (40.2)
>65	24 (14.2)
Mean age ± SD (years)	51.03 ± 14.89
Gender	
Male	81 (47.9)
Female	88 (52.1)
Drug Information	
Total number of medications	1033
Mean number of medications ± SD	6.11 ± 2.03
Clinical Characteristics	
Non-co-morbid Hypertension	47 (27.8)
Co-morbid Hypertension	106 (62.7)
Renal disease stage	
1	6 (3.6)
2	29 (17.2)
3a	20 (11.8)
3b	19 (11.2)
4	47 (27.8)
5	48 (28.4)

Table 2: Drugs that contributed to 90% of the total drug utilized ($DU_{90\%}$)

Drugs	n (%)
Furosemide	118 (11.68)
Lisinopril	91 (9.01)
Amlodipine	75 (7.43)
Ranitidine	70 (6.93)
Hydrochlorothiazide	68 (6.73)
Calcium Carbonate	66 (6.53)
Methyldopa	50 (4.95)
Low dose aspirin	49 (4.85)
Metoclopramide	37 (3.66)
Metolazone	26 (2.57)
Losartan	20 (1.98)
Valsartan	18 (1.78)
Simvastatin	17 (1.68)
Ferrous Sulfate	16 (1.58)
Metformin	14 (1.39)
Humulin	12 (1.19)
Omeprazole	11 (1.09)
Ferrous Fumarate	11 (1.09)
Levofloxacin	11 (1.09)
Hydralazine	10 (0.99)
Atorvastatin	10 (0.99)
Epoetin alfa	10 (0.99)
Gliclazide	9 (0.89)
Spironolactone	8 (0.79)
Tramadol	8 (0.79)
Glimepiride	8 (0.79)
Vitamin B Complex	8 (0.79)
Ferrous Gluconate	8 (0.79)
Ciprofloxacin	8 (0.79)
Metronidazole	8 (0.79)
Vitamin C	7 (0.69)
Acetaminophen	6 (0.59)
Nifedipine	6 (0.59)
Pioglitazone	6 (0.59)
Rabeprazole	6 (0.59)
Dipyridamole	6 (0.59)

and hypertension.[15] In a study among renal failure patients of the nephrology ward in a South Indian tertiary care hospital, calcium channel blockers and beta blockers constituted the major class of drugs involved in interactions.[9]

Also, majority of the patients with stage G4 and G5 had the highest prevalence of the disease, probably because the early stage of CKD is usually asymptomatic thereby making the patients to report to the hospital when the disease has deteriorated to the later stages with symptoms. In the later stages of the disease, patients with renal insufficiency are at high risk of DDIs.[13]

For every additional medication and the presence of hypertension as co-morbidity, there would be increased likelihood of DDI to occur and for the presence of hypertension as co-morbidity with/without any other co-morbidity there would be increased likelihood of DDI to occur. This was similar to a Brazilian study where the probability of one drug interaction increased by 2.5 (95% CI=2.18 to 3.03) times for each additional drug and risk factors strongly associated with drug interactions were obesity, hypertension, diabetes and advanced stage of CKD.[8] The results of multiple linear regression of another study showed a significant positive association between number of potential DDIs with the total number of medications.[16]

The most frequently prescribed drugs were furosemide, lisinopril and amlodipine while the most common potential interaction was lisinopril/furosemide followed by furosemide/calcium carbonate and lisinopril/calcium carbonate. This differed from a Palestinian study where calcium carbonate was most prescribed while calcium carbonate/amlodipine and calcium carbonate/aspirin had the most common potential interaction.[16] Lisinopril could increase serum potassium level while furosemide decreases serum potassium level. These two drugs also have the risk for nephrotoxicity. Renal function monitoring is recommended for patients using medicines that are nephrotoxic. [1] In addition, furosemide is a drug with a high likelihood of causing DDIs.[13]

Some drug-drug interactions can be beneficial.[15] The DDIs do not always suggest exclusion of the implicated drugs from the prescriptions of renal patients. Not all DDIs are harmful.[16] Rather, it could stress the need for appropriate dose adjustments and close monitoring to avoid possible complications such as acute hypotension and renal insufficiency. It should be noted that a potential DDI does not necessarily mean that the patient would have an actual DDI and a clinically significant effect.[17] In some cases, the patient only needs extra monitoring. Metoclopramide/methyldopa was the only serious interaction identified, requiring immediate discontinuation. More than half of the DDIs were significant, requiring close monitoring. This was similar to the results of another study where about 56.7% of the DDIs were significant.[13] Clinical pharmacists have vital roles to play in the early detection of drug-drug interactions. This involves monitoring of patient's medication chart and active participation in clinical ward rounds.[13] Rational prescribing should be practiced to reduce polypharmacy which is one of the major causes of DDIs.[4] Also, physicians and pharmacists should be more aware of these potential

Table 3: Predictors of drug-drug interaction

Model	Independent Variables	Unstandardized Coefficients		Standardized Coefficients		
		B	Standard Error	Beta	t	Sig
Model 1	Constant	-0.460	0.993		-0.463	0.644
	Number of medications	0.947	0.153	0.452	6.208	0.000
Model 2	Constant	-1.589	1.101		-1.443	0.151
	Number of medications	0.965	0.151	0.461	6.406	0.000
	Hypertensive patients	1.467	0.652	0.162	2.249	0.026

*Dependent variable: drug-drug interaction

Table 4: Drug-Drug Interactions Based on Medscape Classification

Category	n (%)
Serious	35 (3.90)
Significant	576 (64.14)
Minor	287 (31.96)

Table 5: Interacting drug combinations

INTERACTING DRUGS	n (%)
Lisinopril_Furosemide	63 (8.08)
Furosemide_Calcium carbonate	49 (6.28)
Calcium carbonate_Lisinopril	40 (5.13)
Furosemide_Hydrochlorothiazide	31 (3.97)
Calcium carbonate_Amlodipine	30 (3.85)
Aspirin_Furosemide	28 (3.59)
Aspirin_Lisinopril	27(3.46)
Furosemide_Metolazone	23 (2.95)
Lisinopril_Aspirin	23 (2.95)
Aspirin_Hydrochlorothiazide	21 (2.69)
Hydrochlorothiazide_Aspirin	20 (2.56)
Hydrochlorothiazide_Ranitidine	17 (2.18)
Calcium carbonate_Aspirin	13 (1.67)
Hydrochlorothiazide_$CaCO_3$	13 (1.67)
Losartan_Furosemide	13 (1.67)
Calcium carbonate_Ferrous sulfate	12 (1.54)
Ferrous sulfate_Calcium carbonate	12 (1.54)
Losartan_Hydrochlorothiazide	9 (1.03)
Aspirin_Valsartan	8 (1.03)
Metoclopramide_Methyldopa	8 (1.03)
Metolazone_Calcium carbonate	8 (1.03)
Calcium carbonate_Ferrous fumarate	8 (1.03)
Fe fumarate_Calcium carbonate	8 (1.03)
Valsartan_Aspirin	8 (1.03)
Valsartan_Furosemide	8 (1.03)
Valsartan_Hydrochlorothiazide	8 (1.03)
Hydrochlorothiazide_Metformin	7 (0.90)
Losartan_Aspirin	7 (0.90)
Spironolactone_Furosemide	6 (0.77)
Ferrous sulfate_Methyldopa	6 (0.77)
Furosemide_Thiamine	6 (0.77)
Ranitidine_Ferrous sulfate	5 (0.64)
Furosemide_Digoxin	5 (0.64)
Hydrochlorothiazide_Glimepiride	5 (0.64)
Losartan_Metolazone	5 (0.64)
Lisinopril_Glimepiride	5 (0.64)
Lisinopril_ Spironolactone	5 (0.64)

Table 6: Drugs that affect serum potassium level

Drugs that Affect Serum Potassium Level	n (%)
Drugs that Increase Serum Potassium Level	
Lisinopril	91 (59.48)
Losartan	20 (13.07)
Valsartan	18 (11.76)
Spironolactone	8 (5.23)
Propranolol	6 (3.92)
Ramipril	3 (1.96)
Enalapril	2 (1.31)
Telmisartan	2 (1.31)
Irbesartan	1 (0.65)
Candesartan	1 (0.65)
Atenolol	1 (0.65)
Drugs that Decrease Serum Potassium Level	
Furosemide	118 (44.03)
Hydrochlorothiazide	68 (25.37)
Aspirin	49 (18.28)
Metolazone	15 (5.60)
Insulin	13 (4.85)
Torsemide	4 (1.49)
Prednisolone	1 (0.37)

Table 7: Nephrotoxic drugs

Nephrotoxic Drugs	n (%)
Furosemide	118 (25.65)
Lisinopril	89 (19.35)
Amlodipine	71 (15.43)
Aspirin	49 (10.65)
Losartan	20 (4.35)
Valsartan	18 (3.91)
Metformin	14 (3.04)
Levofloxacin	12 (2.61)
Omeprazole	10 (2.17)
Spironolactone	8 (1.74)
Rabeprazole	7 (1.52)
Digoxin	6 (1.30)
Ciprofloxacin	6 (1.30)
Nifedipine	5 (1.09)
Torsemide	4 (0.87)
Ofloxacin	4 (0.87)
Hydralazine	4 (0.87)
Cefpodoxime	4 (0.87)
Enalapril	3 (0.65)
Ramipril	2 (0.43)
Cefixime	2 (0.43)
Carvedilol	1 (0.22)
Telmisartan	1 (0.22)
Candesartan	1 (0.22)
Irbesartan	1 (0.22)

interactions and better counsel patients to ensure the informed use of drugs.[16] The monitoring of potential DDIs may promote both rational prescribing and dispensing and it might show the need for education focused on appropriate prescribing.[17] Electronic drug interaction tools should be available in the pharmacy section of hospitals, besides reference books, journals, textbooks and the availability of the internet. Further research works should be conducted to minimize the prevalence of negative drug-drug interactions especially those that could lead to nephrotoxicity.

This study was limited by coverage as data were obtained from only one site. Although, UNTH is a teaching hospital and large referral Centre, the results may not be generalized to other hospital settings. The DDIs presented here were mainly potential not actual drug-drug interactions. It should be noted that a potential DDI does not necessarily mean that the patient would have an actual DDI and a clinically significant effect.[17] In some cases, the patient only needs extra monitoring.

CONCLUSION

Furosemide and lisinopril were the most frequently prescribed drugs to CKD patients who were mainly in renal disease stage 4 or 5. Most of the drug-drug interactions were significant. The major predictors of drug-drug interactions were the number of medications the patients were taking and the presence of hypertension as co-morbidity. The most common interactions were between lisinopril and furosemide; furosemide and calcium carbonate; lisinopril and calcium carbonate. Lisinopril and furosemide were the most frequently prescribed drugs that could increase and decrease serum potassium levels, respectively. Furosemide, lisinopril and amlodipine were the most frequently prescribed drugs that were nephrotoxic.

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