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ORIGINAL ARTICLE

Evaluation of potential drug–drug interactions among patients with chronic kidney disease in northeastern Nigeria

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ABSTRACT

Background: Potential drug–drug interactions (pDDIs) may not manifest clinically in patients who are treated with multiple pharmaceutical agents, but when they do they can produce adverse outcomes. In patients with chronic kidney disease (CKD), the frequent use of multiple agents to manage this condition and its complications puts these patients at increased risk for DDIs. We determined the prevalence of pDDIs in CKD patients in two Nigerian hospitals and investigated possible predictors of pDDIs.
Methods: This cross-sectional study involved patients with CKD who attended the nephrology unit of the University of Maiduguri Teaching Hospital and the medical outpatients clinic of the State Specialist Hospital in Maiduguri, Nigeria. We collected prescriptions, clinical data and laboratory data from the medical files of patients seen between January 2013 and December 2017. Descriptive and inferential statistics were used to analyse the data.
Results: The study included 201 patients. A total of 273 pDDIs were identified in 166 patients (83%). These pDDIs included 30 unique drug interactions, the most common being between ferrous sulphate and calcium carbonate (seen in 46% of patients with pDDIs), followed by lisinopril and furosemide (8%). The proportion of clinically significant interactions was only 2%. There was a positive association between pDDIs and the total number of drugs prescribed ($P < 0.001$).
Conclusions: A high prevalence of pDDIs was documented among Nigerian patients with CKD. The bulk of the interactions were related to the co-prescription of ferrous sulphate and calcium carbonate. The total number of drugs prescribed was a significant predictor of pDDIs. We recommend routine screening of prescriptions of CKD patients for potential pDDIs.

Keywords: chronic kidney disease; potential drug–drug interactions; Nigeria.

INTRODUCTION

Chronic kidney disease (CKD) is one of the main global health problems, especially in developing nations. Its prevalence in Nigeria ranges from 6% to 12% [1-4]. Patients with CKD are at increased risk for drug–drug interactions (DDIs) because of the use of multiple pharmaceutical agents and alterations in their pharmacodynamics and pharmacokinetics [5]. Not all potential DDIs (pDDIs) may manifest clinically, but when they do they can produce adverse outcomes such as treatment failure or drug-induced toxicity with resultant increased costs, morbidity and even mortality [6-9]. The pDDI refers to the likelihood of a drug altering the effects of another when both are administered simultaneously [10]. The reported prevalence of pDDIs in CKD populations ranges from 76% to 89% [11-16]. This underscores the need for clinicians to always screen for pDDIs in this high-risk population.

As kidney function deteriorates in patients with CKD, more medications are needed to control the many complications of this disease, such as metabolic and bone disorders, anaemia, dyslipidaemia and cardiovascular disorders [6]. The main factor associated with pDDIs in CKD patients is, therefore, polypharmacy [17].

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An earlier study on pDDIs among CKD patients in the southwestern part of Nigeria reported a high prevalence of 96% [18], while another study from the southeastern part of the country reported a prevalence of 64.0% [17]. We aimed to determine the prevalence and predictors of pDDIs among CKD patients in northeastern Nigeria.

METHODS

This study was a cross-sectional audit of the prescriptions of CKD patients who attended the nephrology unit of the University of Maiduguri Teaching Hospital and the medical outpatients unit of the State Specialist Hospital in Maiduguri, Nigeria, from January 2013 to December 2017. All patients diagnosed with CKD (stages 1–5, including those on dialysis), who had at least two oral medications concurrently prescribed, comprised the study population.

Data extracted from the patients' medical files included their demographic information, concurrent medications, and clinical characteristics such as comorbidities (other chronic diseases) and last recorded serum creatinine. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation. The eGFR (in mL/min/1.73 m2) was used to group patients into different CKD stages: stage 1, eGFR ≥ 90; stage 2, eGFR 60–89; stage 3a, eGFR 45–59; stage 3b, eGFR 30–44; stage 4, eGFR 15–29; stage 5, eGFR < 15 [19]. Each patient's list of medications was screened using the Omnio® drug interaction checker [20]. The identified pDDIs were graded according to their level of severity. Each pDDI was categorized as "moderate" (use only in special circumstances), "severe" (potential for serious interactions – regular monitoring required or use of alternative medication) or "contraindication" (should be avoided; the risk outweighs the benefit).

Descriptive statistics (frequency, percentage, mean ± standard deviation (SD), range) were used to summarize the data. Comparisons among patients with and without pDDI were performed using the chi-square test for categorical variables and Student's t-test for numerical variables. Multiple linear regression was used to investigate the predictors of pDDIs. A P value < 0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS) for Windows® version 21.0 (SPSS Inc, Chicago, USA) was used for the analyses.

The Research and Ethics Committees of the study hospitals granted the ethical clearance with approval numbers UMTH/REC/17/118 and SSH/GEN/641.

RESULTS

Table 1 presents the demographic data of the study population. There were 201 CKD patients included, with 66% being female. Most were between 40–59 years old and the mean age was 49.5 years. Hypertension (35%) was the most common comorbidity encountered and about 70% of the patients were at CKD stage 5. Four hundred and twenty-eight prescriptions containing at least two concurrent prescribed oral medications were examined. Most patients (85%) used 5 or more drugs with a mean of 5.8 ± 1.5 and a range of 2–9 drugs.

Two hundred and seventy-three pDDIs were observed in 166 (83%) patients. The mean number of pDDIs per patient in this group was 1.4 ± 1.0, with a range of 1–5. The majority (87%) had one or two pDDIs, and only 1.2% had 5 pDDIs (Figure 1).

Of the 273 pDDIs, 98% were of moderate severity, 0.4% were severe interactions, and 1.8% were for contraindicated drug combinations. We identified 30 different drug interacting combinations, ferrous sulphate plus calcium carbonate (in 46%) being the most frequent combination encountered. The prevalence of highly clinically significant interactions was only 1.8%. The pDDIs identified by this study and their potential adverse outcomes are listed in Table 2.

Multiple linear regression analysis (Table 3) revealed a positive relationship between the number of pDDIs and the total number of drugs prescribed (P < 0.001).

DISCUSSION

This study found a high prevalence of pDDIs in our CKD population, with most being of moderate severity and few of high clinical importance. The number of medications prescribed for each patient was a major predictor of pDDIs.

In our study, the prevalence and severity of pDDIs in CKD patients was similar to that reported by an earlier study conducted in the southwestern part of the country [18]. That study also reported a low prevalence of contraindicated drug combinations (0.1%) [18]. A similar prevalence has been reported in India, Palestine and Pakistan [12-14] whereas lower prevalence rates have been reported in Brazil and India (56.9% and 66.8%, respectively) [11,21]. Variations in the prescribing habits of physicians across countries and hospitals could be responsible for this observed difference. Regarding the severity of pDDIs, studies from many countries have reported high rates of pDDIs of moderate severity [11,12,14-16].

The mean number of pDDIs per affected patient recorded by our study is similar to the 1.5 reported in an earlier investigation from the southwestern part of the country [18],

Table 1. Distribution of patients with CKD by occurrence of potential drug–drug interactions (pDDIs).

Variable	All patients n = 201 (%)	With pDDIs n = 166 (%)	Without pDDIs n = 35 (%)	P value
Hospital category				
Secondary	100 (49.8)	74 (44.6)	26 (74.3)	0.001
Tertiary	101 (50.2)	92 (55.4)	9 (25.7)	
Sex				
Female	133 (66.2)	110 (66.3)	23 (65.7)	0.950
Male	68 (33.8)	56 (33.7)	12 (34.3)	
Age in years	49.5 ± 14.5	48.9 ± 14.0	52.1 ± 16.8	0.244
CKD stage				
3	19 (9.5)	17 (10.2)	2 (5.7)	0.309
4	43 (21.4)	38 (22.9)	5 (14.3)	
5	139 (69.2)	111 (66.9)	28 (80.0)	
Number of comorbidities				
None	95 (47.3)	9 (5.4)	2 (5.7)	0.016
1	95 (47.3)	71 (42.8)	24 (68.6)	
≥2	11 (5.5)	86 (51.8)	9 (25.7)	
Number of drugs (SD)	5.8 (1.5)	6.1 (1.3)	4.5 (1.5)	< 0.001
Range	2–9	3–9	2–8	

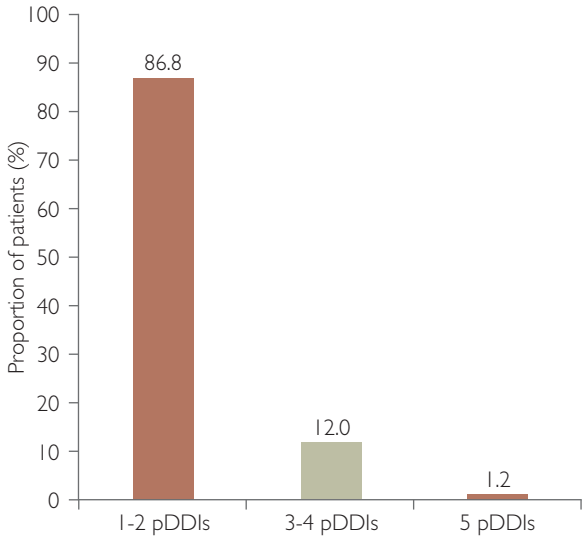

Figure 1. Distribution of patients with one or more potential drug–drug interactions (pDDIs).

but lower than the range of 2.7–4.1 reported in other studies [12,15,21]. The differences from studies outside Nigeria may relate to variations in the prescribing habits of physicians of different nations.

The most frequent interacting drug combinations identified in our study was calcium carbonate and ferrous sulphate. Concomitant use of calcium may decrease the intestinal absorption of orally administered iron. Therefore, when these two drugs are co-prescribed for CKD patients, physicians and pharmacists should counsel these patients to take the ferrous sulphate at least two hours apart from the calcium carbonate, to prevent this unwanted interaction. This finding is in agreement with some studies [11,16,18], but differs from others, which reported ascorbic acid/cyanocobalamin, calcium carbonate/amlodipine, ferrous sulphate/omeprazole, lisinopril/furosemide, or aspirin/clopidogrel as the most frequent combinations for pDDIs [12-14,17,21].

The number of prescribed medications was a significant predictor of pDDIs in our study, consistent with the results of others [14,17,22]. Physicians prescribing medications for these patients should ensure rational prescribing and avoidance of unnecessary medications to reduce the pill burden and the risk of DDIs in this patient population. The use of clinical decision support systems could assist in this regard. Clinical pharmacists should also screen prescriptions for pDDIs before dispensing medications to CKD patients and, when minor or moderate interactions are detected, patients should be counselled on how to separate the administration of the drugs that are involved.

Table 2. Potential drug–drug ınteractions among patients with chronic kidney disease.

Severity level	Object drug_precipitant drug	n (%)	Potential adverse outcomes
Contraindication* N = 5 (1.8%)	coartem_ciprofloxacin	5 (1.8)	Increased risk of QTc-interval prolongation and life-threatening cardiac arrhythmias
Severe N = 1 (0.4%)	erythromycin_amlodipine	1 (0.4)	Increased risk of hypotension, shock, acute kidney failure, and sudden death
Moderate N = 267 (97.8%)	ferrous sulphate_calcium carbonate	125 (45.8)	Decreased absorption of iron
	lisinopril_furosemide	21 (7.7)	Severe postural hypotension
	captopril_furosemide	18 (6.6)	Severe postural hypotension
	captopril_spirinolactone	18 (6.6)	Hyperkalaemia
	ciprofloxacin_ferrous sulphate	14 (5.1)	Decreased effectiveness of ciprofloxacin
	ferrous sulphate_antacid	14 (5.1)	Decreased absorption of iron
	methyldopa_ferrous sulphate	10 (3.7)	Decreased efficacy of methyldopa
	ciprofloxacin_calcium carbonate	7 (2.6)	Decreased effectiveness of ciprofloxacin
	lisinopril_aspirin	7 (2.6)	Decreased antihypertensive effects of lisinopril
	diclofenac_furosemide	5 (1.8)	Decreased antihypertensive and diuretic actions of furosemide
	lisinopril_ spirinolactone	4 (1.5)	Hyperkalaemia
	ciprofloxacin_antacid	3 (1.1)	Decreased effectiveness of ciprofloxacin
	captopril_aspirin	2 (0.7)	Decreased antihypertensive effects of captopril
	captopril_diclofenac	2 (0.7)	Decreased antihypertensive effects of captopril and deterioration of renal clearance
	levofloxacin_ferrous sulphate	2 (0.7)	Decreased effectiveness of levofloxacin
	lisinopril_torsemide	2 (0.7)	Severe postural hypotension
	losartan_furosemide	2 (0.7)	Severe postural hypotension
	atenolol_nifedipine	1 (0.4)	Increased toxic effects of both drugs
	atenolol_prazocin	1 (0.4)	Increased hypotensive action of prazocin
	cefuroxime_calcium carbonate	1 (0.4)	Decreased efficacy of cefuroxime
	ciprofloxacin_multivitamins	1 (0.4)	Decreased effectiveness of ciprofloxacin
	digoxin_furosemide	1 (0.4)	Increased arrhythmias
	levofloxacin_calcium carbonate	1 (0.4)	Decreased effectiveness of levofloxacin
	levofloxacin_multivitamins	1 (0.4)	Decreased effectiveness of levofloxacin
	lisinopril_diclofenac	1 (0.4)	Decreased antihypertensive effects of lisinopril
	lisinopril_naproxen	1 (0.4)	Decreased antihypertensive effects of lisinopril
	phenytoin_calcium carbonate	1 (0.4)	Decreased levels and effectiveness of phenytoin
	risperidone_levofloxacin	1 (0.4)	Increased risk of QTc-interval prolongation and arrhythmias

* Interaction which is highly clinically significant. Use of this drug combination is contraindicated.

Table 3. Multivariable analysis of factors associated with number of potential drug–drug interactions.

Variable	Coefficient	P value	95% confidence interval	
Hospital category	0.016	0.830	–0.263	0.328
Number of drugs prescribed	0.409	< 0.001	0.184	0.394
Number of comorbidities	0.134	0.051	–0.001	0.313

Among the limitations of our study is the fact that we detected only pDDIs, which may not manifest clinically. Another is that the Omnio® drug interaction checker used does not take into consideration the prescribed dose, frequency of administration, route of administration, and duration of medication use.

CONCLUSIONS

There is a relatively high prevalence of pDDIs among patients with CKD in northeastern Nigeria. Most were of moderate severity, and the most common was between calcium carbonate and ferrous sulphate. The number of medications prescribed for each patient was a significant predictor of pDDIs and we therefore recommend that physicians and pharmacists attending to these patients should use clinical decision support systems or drug–drug interaction software to detect and prevent detrimental pDDIs.

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