Evaluation of Potential Drug-Drug Interactions and Association with Adverse Drug Reactions in Predialysis Chronic Kidney Disease Patients at Indonesian National Referral Hospital

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ABSTRACT

Background: *Chronic kidney disease (CKD) is often accompanied by a variety of comorbidities that require several medications thus, polypharmacy is unavoidable. One of the consequences of polypharmacy is the occurrence of potential drug-drug interactions (DDI). The aim of this study is to evaluate the profile of DDI in pre-dialysis CKD patients and to identify the possible adverse drug reactions (ADR) due to DDI.* ***Methods****: This cross-sectional study includes stage 3-5 pre-dialysis CKD patients at a referral hospital in Indonesia in 2019 – 2020. Data were collected from the electronic health record and the hospital's medical record. The prescriptions were analysed for potential DDI using Micromedex software and ADRs assessment through clinical symptoms and laboratory data abnormalities.* ***Results****: A total of 106 patients were included in the study, around 60 (56.6%) patients received more than six medications. There were 111 types of medications prescribed with the most frequently prescribed drug was bisoprolol (36.5%). The proportion of patients who received treatment with a potential DDI was 76% (81 patients), while the proportion of patients who experienced ADR was 28% (23 patients). The most prevalent ADRs were hyperglycaemia, hypertension, hyperkalaemia, and hypotension. Cardiovascular disease had a statistically significant relationship with ADR suspected due to DDI (p = 0.03).* ***Conclusion****: A significant number of potential DDI were seen in the prescriptions of stage 3-5 pre-dialysis CKD patients at a referral hospital in Indonesia between 2019 – 2020. Cardiovascular disease was identified as the most common risk factor for ADR suspected caused by DDI.*

Keywords**:** *contraindications, adverse reactions, kidney insufficiency, dialysis, drug toxicity.*

INTRODUCTION

Chronic kidney disease (CKD) is considered a global health problem with an increasing incidence and prevalence of kidney failure, poor prognosis and high treatment costs. Hill et al., found that the global prevalence of CKD was 13.4% and according to Global Burden of Disease, CKD was the 12th leading cause of death worldwide. In Indonesia, the prevalence of CKD in 2018 has doubled compared to 2013 to becoming 0.38%.[1-3] CKD can be classified into stages 1-5, where usually patients at stage one or two do not experience significant symptoms or other metabolic disorders, but symptoms can be seen if CKD patients has entered stages 3 to 5 such as uremic symptoms, anaemia, malnutrition as well as fluid and electrolyte abnormalities.[4]

Almost all patients with CKD have

comorbidities such as hypertension and diabetes mellitus, so it is necessary to use various drug combination therapies that can lead to polypharmacy. The consequences of polypharmacy are poor patient medication adherence due to the large number of drugs, increased treatment costs, and the occurrence of potential drug-drug interactions (DDI). DDI can actually cause beneficial effects but can also be detrimental/unwanted. Unwanted DDI may result in therapeutic failure/reduced therapeutic effect (antagonistic interactions) or increased toxicity (synergistic/additive interactions).[5-7] Previous study has revealed that the prevalence of DDI in CKD patients ranged between 76.1% and 89.1%.[7] DDI is considered a preventable treatment problem but in clinical practice it can result in adverse drug reaction (ADR), thereby increasing the risk of hospitalization and higher health care costs.

Based on several studies, the estimates proportion of patients who experience DDI and have the potential to cause ADR is between 0.63 and 56%.[8] Rama et al., have demonstrated that the risk of ADR due to drug interactions that often occur in CKD patients are hypotension, hypoglycaemia, and hyperkalemia.[9] In addition, Rodrigues and Oliveira stated that DDI and ADR are often the consequences of polypharmacy and are associated with factors such as patient's gender, age, diagnosis, comorbidities, and using certain types of drugs.[10] The amount and severity of ADR is also said to increase with the increasing number of drugs taken.[11] CKD patients usually also experience changes in pharmacokinetic and pharmacodynamic parameters that can impact its treatments. The various impacts of these changes are reduced drug excretion by the kidneys, decrease drug absorption due to gastrointestinal oedema, and increased volume of distribution due to fluid retention.[12] Hence, this study is planned to assess the profile of DDI in the medications prescribed to stage 3-5 pre-dialysis CKD patients and also to identify the possible ADR due to DDI. We believe that the evaluation related to the use of drugs is important in the hope of minimizing the occurrence of drug interactions that can cause ADR in patient's therapy.

METHODS

This cross-sectional study included male and female stage 3-5 pre-dialysis CKD patients ages above 18 years who attended Outpatient Department of Cipto Mangunkusumo Hospital. The study was performed after the approval from the Institutional Ethics Committee, Universitas Indonesia (#241/UN2.F1/ETIK/PPM.00.02/2021). Data were collected for a duration of 1 year (2019 – 2020), from patients' medical records and electronic health records. The data collected included the age of the patient, gender, subjective complaints, abnormal physical examination, comorbid diseases, number of drugs given, and drug doses. The medications prescribed to the patients were noted and analysed for potential DDIs.

A sample size of 106 was calculated considering confidence interval of 95% and an absolute precision of 5% and the prevalence of DDIs as 50%.[13] The prescriptions were analysed for the potential drug interactions using Micromedex software. This software provides the severity, risk rating, and the summary of DDIs. The drugs interactions are explained by its mechanism and its potential effects. The assessment of ADR due to drug interactions, will be seen from the clinical manifestations and abnormalities in the patient's laboratory results during the last 3 months of follow-up, documented in the medical record and EHR (Electronic Health Record). The severity of ADRs is categorized into mild, moderate, and major based on Hartwig scale. ADRs were considered mild or moderate if it does not require discontinuation of treatment, whereas ADRs were considered major if they required immediate medical attention, resulted in long-term damage to the patient, or caused death.[14]

Data analysis consisted of descriptive and analytical analysis. Statistical analysis was performed using SPSS version 20.0. The analysis used to determine the relationship between variables using Chi-square test and logistic regression (p value <0.05 was considered statistically significant).

RESULTS

A total of 206 CKD patient medical records were collected and106 patients met the inclusion criteria. Patients who do not meet the inclusion criteria are patients that has incomplete data (**Figure 1**). The subjects of this study were dominated by male patients with the highest distribution of age groups being >65 years of age. The majority of the subjects were patients with stage three and the most common comorbid diseases were hypertension and DM. In addition to the comorbidities listed in the Table 1, 88.7% of patients also had other comorbidities such as benign prostate hyperplasia, Parkinson's disease, obesity, osteoarthritis, SLE, asthma, TB, HIV and dyspepsia. Most of the patients used 6-10

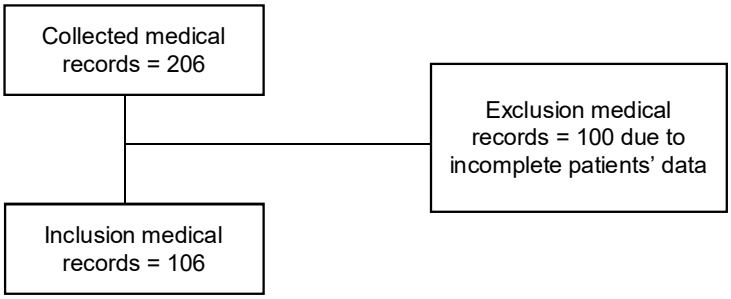

Figure 1. Flowchart sample collection.

Table 1. Baseline characteristics

Characteristics	N (%)
Sex	
- Male	60 (56.6)
Age (year)	
- 18 – 40	7 (6.6)
- 41 – 65	47 (44.3)
- > 65	52 (49.1)
CKD stage	
- Stage 3	71 (67)
- Stage 4	31 (29.2)
- Stage 5 pre-dialysis	4 (3.8)
Comorbid	
- Hypertension	69 (65.1)
- Diabetes mellitus	38 (35.8)
- Heart disease	53 (50)
- Hepatitis	9 (8.5)
- Hyperuricemia	38 (35.8)
- Others	94 (88.7)
Number of drugs	
- ≤ 5	19 (17.9)
- 6 – 10	60 (56.6)
- > 10	27 (25.5)
Antihypertensive drugs	
- CCBs (Amlodipine, Diltiazem, Nifedipin)	30 (28.3)
- ACEi (Lisinopril, Ramipril)	18 (17)
- ARBs (Candesartan, Irbesartan, Telmisartan, Valsartan)	56 (52.8)
- Beta-blockers (Bisoprolol, Carvedilol, Propranolol)	50 (47.2)
- Alpha blockers (Tamsulozin, Terazosin)	15 (14.2)
- Diuretics (Furosemid, Spironolactone, Hydrochlorotiazid)	35 (33)
- Nitrate (Nitroglycerine, ISDN)	18 (17)
- Oral antidiabetics	
- Sulphonylureas	28 (26.4)
- Biguanid	9 (8.5)
- Thiazolidinedione	5 (4.7)
- Alpha glucosidase inhibitors	5 (4.7)
- Insulin	38 (35.8)
Statins	55 (51.9)

types of drugs. Angiotensin receptor blockers and sulfonylureas are the most commonly prescribed antihypertension and antidiabetic, respectively (**Table 1**).

A total of 124 potential drug interactions were seen in 106 patients, most of them were in moderate category (**Table 2**). Potential drug interactions with major and moderate categories were listed in **Table 3**.

The proportion of patients receiving treatment with a potential DDI was 81 out of 106 patients (76%) (**Table 4**). Twenty-three out of 81 (28%) patients experienced ADR which was suspected due to DDI (**Table 4**).

The most frequently complained ADRs include hyperglycaemia and hypertension followed by hyperkalaemia and hypotension (**Figure 2**).

Table 2. Category of DDIs

Category of DDIs	N=124 (%)
Major	49 (39.5)
Moderate	72 (58.1)
Minor	3 (2.4)

Table 4. Proportion of patients with DDIs and ADRs

Proportion of patients	N (%)
Proportion of patients with DDIs	81 (76)
Proportion of patients with ADRs	23 (28)

Table 3. Medication pairs involved in major and moderate category drug interactions

Medication pairs	Category of DDIs	Frequency of DDIs, N=106 (%)	Effect of drug interaction
Clopidogrel-Lansoprazole	Major	9.4	Lansoprazole may reduce clopidogrel effect
Amlodipine-Simvastatin	Major	8.5	Amlodipine increases simvastatin concentrations, increasing the risk of myopathy and rhabdomyolysis
Acetylsalicylic acid-Furosemide	Major	8.5	Acetylsalicylic acid may cause a decrease in the effectiveness of furosemide
Bisoprolol-Insulin	Moderate	14.2	Bisoprolol can mask the symptoms of insulin-induced hypoglycaemia
Acetylsalicylic acid-Bisoprolol	Moderate	13.2	Acetylsalicylic acid decreases the effect of bisoprolol
Acetylsalicylic acid-Nitroglycerin	Moderate	8.5	Acetylsalicylic acid can increase the concentration of nitroglycerine enhance antihypertensive effect
Furosemide-Insulin	Moderate	8.5	Furosemide decreased glucose sensitivity to insulin in skeletal muscle via glucose transport inhibition

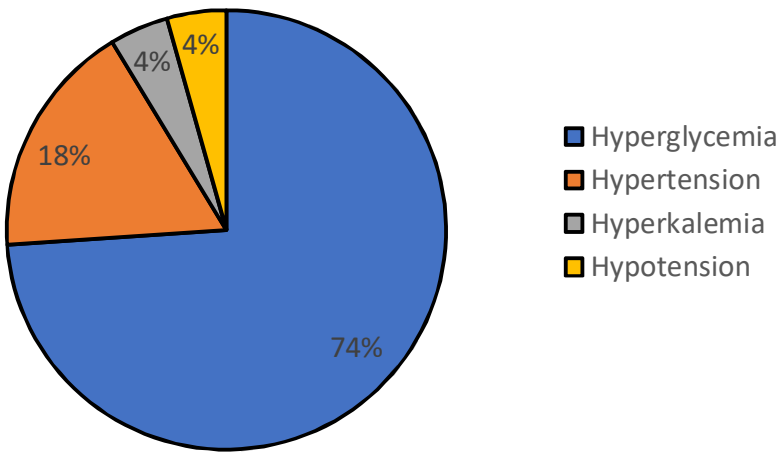

Figure 2. Proportions of ADRs suspected caused by DDIs

Table 5. Predictors of DDIs (multivariate logistic regression analysis)

Variables	Groups	Patients with ADRs	Patients without ADRs	OR (95% CI)	*p* value
Gender	Male	16	44	1.48 (0.49 – 4.4)	0.48
	Female	7	39		
Number of drugs used	>10	12	14	2.83 (0.94 – 8.51)	0.06
	<10	11	69		
Type of comorbidities	Cardiovascular disease	15	23	3.3 (1.1 – 9.6)	0.03*
	Diabetes mellitus	19	42	2.5 (0.71 – 8.85)	0.15
	Dyslipidemia	15	38	1.9 (0.65 – 5.58)	0.24

Logistic regression analysis showed that cardiovascular disease comorbidities was associated with the presence of drug interactions (OR = 3.3; 95%CI = 1.1 – 9.6; p = 0.03) (**Table 5**).

DISCUSSION

CKD patients are one of the most drug users because they are often accompanied by comorbid diseases. As CKD patients often receive multiple medications, potential DDIs are common in this population. Harmful DDIs will increase the risk of ADRs. Several methods can be used to assess DDIs, one of which is Micromedex which is used in this study. Our study showed that the proportion of patients with DDIs was 76% of which the majority were in the moderate severity. The most frequent DDIs in the present study were between bisoprolol and insulin as well as between lansoprazole and sucralfate. Our study has also noted that 23 out of 81 patients with DDIs had ADRs with the most ADRs being hyperglycaemia and having cardiovascular diseases was identified as the most common risk factor.

Hypertension and diabetes mellitus were the two most common comorbidities. This finding is in line with previous studies and global data, which stated that hypertension and diabetes mellitus were the two most common diseases in CKD patients.[15] Several literatures have demonstrated that high blood glucose levels in diabetics can cause blood vessels damage including in the kidney which results in the disruption of kidney function. In addition, uncontrolled hypertension will cause the narrowing, weakening, and hardening of renal artery.[2,16,17] Therefore, in the present study, we demonstrated that bisoprolol was the most commonly prescribed drug in CKD patients, followed by allopurinol, vitamin B12, and folic acid. Previous study has shown that beta-blockers have a beneficial effect on endothelial function as well as a protective effect on the kidneys.[16] The second drug that is often prescribed in this study was allopurinol. It has been proven that in CKD patients, there is a decreased urinary excretion of uric acid which leads to the development of hyperuricemia.[18] Goicoechea et al. have shown that allopurinol can reduce C-reactive protein and slow the progression of kidney disease in CKD patients with eGFR < 60 mL/min as well as reduce cardiovascular and hospitalization risk.[19] To alleviate anaemia that often accompanies CKD, vitamin B12 and folic acid were given in this study. Meriyani, et al., have demonstrated that the use of antianemia in CKD patients could increase the level of haemoglobin in patients with CKD.[20] Approximately 80-90% of CKD patients have anaemia due to erythropoietin deficiency, iron deficiency, blood loss, shortened erythrocyte life span, folic acid deficiency, and acute and chronic inflammatory processes.[21]

In the present study we found that the proportion of patients with DDIs was 76% of which the majority were in the moderate severity. The results of our study were in line with the study conducted by Saleem et al. (2017) in Pakistan which showed that the proportion of patients experiencing DDIs was 78.5% and were dominated by the moderate severity.[22] In our study, 57% of patients had more than eight medications with a median of 2-20 medications in their prescription. Previous studies have also demonstrated that the majority

of patients of CKD received around 6-10 kinds of medications.[7, 23] In fact, this polypharmacy is an unavoidable matter in patients with CKD due to the high risk of factors, comorbidities, and complications. Therefore, it is necessary to give a combination of medications though still have to consider the risk-benefit in each patient.

Altogether there were 124 types of potential interactions in this study. This number was much lower when compared to a previous study in Nigeria which contained 405 types of potential interactions.[7] The most frequent DDIs in this study were between bisoprolol and insulin and between lansoprazole and sucralfate (14,2%). Research by Rama et al (2012) in India found that the DDI with the highest frequency was ascorbic acid with cyanocobalamin with a percentage of 12.4%.[9] There maybe a few reasons why this study has varied DDI results compared to previous studies such as only focused on pre-dialysis patients and only includes outpatients. These reasons can affect the type of drug given which will then affect the DDIs that appears.

Our study has noted that 23 out of 81 patients (28%) were suspected of having ADR due to DDIs with the most frequent ADR were hyperglycaemia and hypertension, followed by hyperkalaemia and hypotension. The most frequent DDIs that causes hyperglycaemia were between furosemide and insulin (6 patients) as well as bisoprolol and insulin (5 patients). The interaction between furosemide and insulin is cause by a decrease in glucose sensitivity to insulin in skeletal muscle through inhibition of glucose transport. However, this interaction was only seen in *in-vitro* studies.[24] The mechanism of interaction between bisoprolol and insulin through inhibition of beta-2 adrenoceptors in pancreatic islet cells to produce insulin by beta-blockers such as bisoprolol.[25,26]

Hyperglycaemia in this study was defined on the basis of HbA1C values after three months of treatment, fasting blood glucose levels, and blood glucose levels 2-hours after post prandial. In patients suspected of having hyperglycaemia due to DDI, HbA1C levels ranged from 7.2 - 9%, fasting blood glucose levels ranged from 126-263 mg/dL, and blood glucose levels 2-hours post prandial were between 155-263 mg/dL. The above interactions indicate the need for monitoring blood glucose levels so that the clinical significance of the interactions can be assessed.

In this study there were four patients who experienced hypertension suspected due to DDI. DDIs between tacrolimus and diltiazem also tacrolimus and omeprazole were experienced by one patient each. Their blood pressures were 150/80 and 143/88 mmHg, respectively, which were measured after taking the drug for three months. The mechanism of those two interactions were through the inhibition of the CYP3A enzyme by diltiazem and omeprazole. This can cause an increase in the concentration of tacrolimus which leads to hypertension that can occur in 50% of patients receiving tacrolimus drugs. This finding is supported by an *in-vivo* study by Chiasson et al (2011) which investigated the effect of tacrolimus in wild-type mice at doses of 1 or 10 mg/kg/day. The response was concentration-dependent, in which the administration of the highest concentration of tacrolimus (10 mg/kg/day) results in an increase in systolic blood pressure of 40-50 mmHg.[27]

The other DDIs resulting in hypertension were between mefenamic acid and valsartan and between acetylsalicylic acid and bisoprolol. NSAIDs can reduce the antihypertensive effect of ARBs or beta blockers by decreasing the production of renal prostaglandins. This is consistent with a study in the Netherlands (2015) involving 112 outpatients and after giving NSAIDs for two weeks resulted in >10% of patients experienced an increase in systolic blood pressure (SBP). It has been suggested to monitor the SBP before and after NSAID administration and the need for close monitoring for patients who are prescribed high doses of NSAIDs.[28]

Hyperkalemia was suspected cause by DDI between valsartan and spironolactone. These two drugs have an additive effect which leads to an increase in kalium levels in the blood. Valsartan decreases aldosterone levels which causes kalium retention, while spironolactone is known as a kalium-sparing diuretic. Wrenger et al., (2003) also identified other factors that can increase kalium levels in patients using these two drugs, namely old age, spironolactone

dosage > 25 mg/day, decrease in kidney function, and type 2 diabetes mellitus.[29] In addition, in the present study, hypotension was suspected cause by DDI between N-acetylcysteine (NAC) and nitro-glycerine (NTG). Concomitant use of NAC and NTG may cause a hypotensive effect due to additive vasodilatory mechanisms and an increased risk of NTG to induce headache. Pasupathy, et al (2017) have also shown in their study which involved 112 patients, the incidence of hypotension in the NAC-administered group with NTG was 26%, in which hypotension was defined as SBP <90 mmHg.[30] All of the ADRs above were possible in causality assessment. This was in accordance with Stockley which states that DDI is not the sole cause that can cause side effects to patients.[31]

In this study there was a statistically significant relationship between a few variables and ADR due to DDIs (p value < 0.05). The variables were the numbers of drug used (>10 drugs) and comorbid diseases. Saleem et al., (2017) stated that there was a significant relationship between ages (<60 years-old), length of stay (>5 days), number of drugs (>5) and comorbid disease (hypertension) with DDI.[21] To date, there have been no studies that have analysed the relationship of certain variables or confounding variables with ADR caused by DDI.

In this study, cardiovascular disease has a statistically significant relationship with suspected ADR due to DDIs (p = 0.03). This was in line with a study of ADR in CKD patients by Laville, et al (2020) which stated that having a history of cardiovascular disease, using certain amounts of drug, history of acute kidney injury and poor compliance can significantly increase the risk of ADR.[32]

There are several limitations in this study. The first is using a secondary data which only relies in medical records and EHR. Sometimes there were a difference between EHR and the patient's medical records, making it difficult to record accurate treatment. Another limitation was an accurate causality analysis cannot be carried out between DDI and ADR. This is because this study is done retrospectively which means many factors can influence the incidence of ADR due to DDIs, either external or internal factors. Micromedex software has high sensitivity and specificity, but also has its own limitations. The identified DDIs did not consider the dose used, frequency of drug administration, route of drug administration and duration of drug use. These things can affect the potential DDIs that can occur. Besides its limitations, this study also has its advantage which is being the first study to examine the ADR cause by DDI in patients with CKD stage 3-5 pre-dialysis.

CONCLUSION

In patients with CKD stage 3-5 pre-dialysis at referral hospital in Indonesia there were 111 types of drugs prescribed with the most frequently prescribed drug was bisoprolol (36.5%). The proportion of patients receiving treatment with potential DDIs was 76% (81 patients). The proportion of patients with suspected ADR due to DDIs was 28% (23 patients). The ADRs were hyperglycaemia, hypertension, hyperkalaemia and hypotension. There is a statistically significant relationship between the confounding variables, namely, number of drugs, cardiovascular disease and DM with ADR cause by DDI. The multivariate results found that cardiovascular disease had a statistically significant relationship with ADR due to DDIs (p = 0.03).

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