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Dosage Adjustment as an Efficiency in Treatment Costs for Chronic Kidney Disease Patients

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Abstract
Introduction: Chronic Kidney Disease (CKD) treatment, in all stages, has been shown to impose a big economic burden. To reduce drug costs, dose adjustment can be used in CKD treatment. Apart from saving costs, dose adjustments can also reduce the risk of side effects due to excessive doses. This research aimed to identify the dose suitability of CKD patient treatment and calculate the difference in treatment costs before and after the dose adjustments.
Method: This research was a cross-sectional study using descriptive analysis. Data was collected from medical records in UGM Academic Hospital using purposive nonrandom sampling in inpatient CKD patients with decreased creatinine clearance and serum creatinine who underwent hospitalization for at least one year.
Result: There were 58.14% male patients and 41.86% female patients. Most of the patients have stage 5 CKD (46.51%) and hypertension comorbidities (59.30%). Around 69.14% of drugs used in treatment required dose adjustment and only 52.33% of them had appropriate doses based on the Lexicomp Drug Information Handbook. The class of drugs that required the most dose adjustments was antibiotics with 14 occurrences. After the dose adjustment, the saved cost from patients with inappropriate doses was IDR 1,766,330. The biggest cost difference after the dose adjustment was IDR 1,090,865, which comes from the antibiotic group.
Conclusion: Dosage adjustments can reduce the incidence of medication errors, improve clinical outcomes, and increase the effectiveness of clinical outcomes and cost-effectiveness.

Keywords: *Adjustment dose, Chronic Kidney Disease, Cost*

Introduction

The condition of Chronic Kidney Disease (CKD) patients can become worse over time despite their treatment can slow its progression[1,2]. According to data from the Centers for Disease Control (CDC) and Prevention's CKD Surveillance System, the prevalence of CKD stages 1-4 in the United States grew from 11.8% in 1988 to 1994 to 14.2% in 2015–2016. The National Health and Nutrition Examination Survey data revealed that the increase in CKD stage 3-5 prevalence was nonlinear; while it rose between the 1990s and 2000s, it has stayed rather steady ever since[3]. Based on the Global Burden of Disease (GBD) study in 2017 reported that the global prevalence of CKD in women is 1.29 times greater than the risk of developing CKD in men. Another study stated that in the incidence of CKD, as many as 55.40% were women and 44.60% were men[4,5]

Early treatment of CKD is a challenge, as 94.5% of people with CKD are unaware that they have the disease[6,7]. There is a decrease in kidney function, resulting in significant changes in the drug pharmacokinetics with ordinary doses, the drug effect may be increased or decreased. In addition, the patient's response to the drug may also change due to the presence of comorbidities in CKD patients which can cause patients to be more susceptible to the effects of the drug[8]. Adjustment of drug doses in CKD patients is very important to do. If the dose of the drug is not adjusted appropriately in patients with CKD, the concentration of the drug may increase, thus posing a risk of adverse drug reactions. On the other hand, an unnecessary decrease in dosage can result in less treatment and thus may decrease its effectiveness.

Drug dose adjustment brings many benefits to CKD patients, but there are still many CKD patients who don't get appropriate doses. Research in Lebanon shows that 37% of patients received a well-adjusted dose of the drug, 49% with an inadequate dose of 14% not adjusted at all[8]. Research in Nepal shows that 80% of CKD patients have received the appropriate dose of medication while the rest have received the unmatched dose[9]. Research conducted in Jakarta stated that as many as 33.72% of patients received the appropriate dose and 66.72 patients received the inappropriate dose[10]. In addition, there is also a study in Tegal which states that there are 51.78% of patients who receive the appropriate dose for patients with CKD[11].

Dosage regimen adjustments in CKD patients are made to avoid excessive accumulation of drugs or metabolites that can cause serious side effects in

patients with renal impairment. This can lead to irrational use of the drug. The consequences that can arise from irrational use of drugs include reduced quality of treatment which can eventually lead to an increase in patient mortality and morbidity, and lead to an increase in treatment costs[12]. Dose adjustments can be used as an effort to reduce drug prices because drugs are an important component in health service efforts even the use of drugs can reach 40% of all health service costs. Previous research suggests that dose adjustment can save drug costs and may prevent Adverse Drugs Events (ADEs). In the intervention, this number was significantly lower with 49 events ADEs. The intervention resulted in drug cost savings of $2250 US. There are still few studies comparing dose adjustment and cost difference, so further studies are needed to see the cost efficiency if dose adjustment is done in CKD patients. This study aims to analyze the suitability of drug dose use in CKD patients and compare the difference in costs that can be saved if dose adjustments are made in CKD patients.

Materials and Methods

This study was a cross-sectional study with descriptive analysis. Data collection was conducted retrospectively using medical record data of patients with kidney disorders who underwent hospitalization at UGM Academic Hospital for a period of 1 year. In patients with a decrease in creatinine clearance, analysis of the calculation of adjustment dose on treatment has been received. The sampling technique in this study was purposive sampling. The inclusion criteria in this study were all hospitalized patients with reduced creatinine clearance and there was serum creatinine data. The exclusion criteria in this study were *hospitalized CKD* patients with incomplete medical record data and pediatric patients (≤ 12 years). The data taken comes from the medical record of inpatients in the form of medical record numbers, patient names, age, weight, length of treatment, data on the results of patient laboratory examinations, and therapy received by patients including the type of drug, dose, and frequency of drug use, and the cost of drugs received by patients. Analysis of drug dose appropriateness used by CKD patients refers to the literature and guidelines of the Lexicomp Drug Information Handbook. Cost efficiency analysis or cost difference was obtained from the actual cost to the patient minus the cost if dose adjustments are made to the drugs used.

Result

Based on the study, 98 patients were obtained with 86 patients who met the inclusion criteria. There were 58.14% male patients and 41.86% female patients. The level of CKD in this study was dominated by stage 5 as much as 46.51% and stage 1 CKD as much as 19.77%; stage 2 as much as 4.65%; stage 2 as much as 4.65%; stage 3 as much as 12.79% and stage 4 as much as 16.28%. Comorbidities that dominated in this study were hypertension at 59.30%. Other comorbidities are diabetes mellitus (30.23%); CHF (16.28%); IHD (5.81%); infection (9.30%); and others (27.91%). In this study, 69.14% of drugs used required dose adjustment and 30.86% of drugs did not require dose adjustment. A total of 52.33% of the treatment doses used in patients were appropriate based on the guideline and 47.67% of doses were inappropriate based on the Lexicomp Drug Information Handbook. In this study, 41 patients received the inappropriate dose, there were 39 patients with the higher dose and 3 patients received the lower dose.

Table 1. Characteristics of Patients in The Study

Characteristics	Category	Number of patients	
		n (=86)	%
Gender	Man	50	58.14
	Woman	36	41.86
Stage of CKD	1	17	19.77
	2	4	4.65
	3	11	12.79
	4	14	16.28
	5	40	46.51
Comorbid	Hypertensive	51	59.30
	Diabetes Mellitus	26	30.23
	CHF	14	16.28
	IHD	5	5.81
	Infection	8	9.30
	Other	24	27.91
Drug Profile	Requires Dosage Adjustment	56	69.14
	Does not require dose adjustment	25	30.86
Dosage Appropriateness	Appropriate dosage	45	52.33
	Inappropriate dosage	41	47.67

In this study, an antibiotic was the most widely used drug and requires dose adjustment. Some of the antibiotics used by patients in this study were azithromycin, cefadroxil, cefixime, cefotaxime, ceftazidime, ciprofloxacin, gentamicin, and meropenem. The analgesic groups used and require dose adjustment are ketorolac, meloxicam, morphine, paracetamol, and tramadol. Hypertension drugs used

by patients and require dose adjustment are bisoprolol, captopril, lisinopril, and spironolactone. Other drugs that require dose adjustment are allopurinol, tranexamic acid, digoxin, escitalopram, gemfibrozil, metoclopramide, and ranitidine based on the Lexicomp Drug Information Handbook.

Table 2. The type of drug used by the patient and requires dose adjustment

No.	Types of drugs that require dose adjustment based on Clcr value (< 30ml/min)	No.	Types of drugs that require dose adjustment based on Clcr value (< 30ml/min)
1	Allopurinol	14	Gentamicyn
2	Tranexamic Acid	15	Ketorolac
3	Azitromycin	16	Lisinopril
4	Bisoprolol	17	Meloxicam
5	Captopril	18	Meropenem
6	Cefadroxil	19	Metformin
7	Cefixime	20	Metoclopramide
8	Cefotaxime	21	Morphine sulfate
9	Ceftazidime	22	Paracetamol
10	Ciprofloxacin	23	Ranitidine
11	Digoxin	24	Spironolacton
12	Escitalopram	25	Tramadol
13	Gemfibrozil		

There were 40 instances of patients with doses that did not match the guideline for CKD patients. The drug class that needs the most dose adjustment was antibiotics (14 events); anti hyperuricemia and antifibrinolytics there are 7 events; H2 Blocker as many as 5 events. Analgesic class drugs have as many as 4 events that require dose adjustment and 3 events in ACE Inhibitor class drugs.

Table 3. Inappropriate dosage events in the use of drugs requiring dose adjustment

No.	Types of drugs	Number of occurrences
1	Antihiperurisemia	7
2	Antibiotic	14
3	Analgesic	4
4	antifibrinolitik	7
5	H_2 blocker	5
6	ACE Inhibitor	3
	Total	**40**

The difference in costs after dose adjustment was the most savings if adjustments are made in the use of antibiotic drugs. The difference in cost in the antibiotic group was IDR 1,090,865. Another treatment after dose adjustment on antifibrinolytic drugs amounted to IDR 471,240; class H 2 Blocker IDR 123,554; analgesic class drugs amounted to IDR 76,500; ACE Inhibitor class drugs amounted to IDR 2,121; and anti-hyperuricemia class drugs IDR 1,950. The total difference in overall costs that can be saved if dose adjustments are made on treatment was IDR 1,766,230. Dose discrepancies in antibiotic use are still high. In this study, there were 14 instances of inappropriate doses in the use of antibiotics.

Drug cost efficiency was obtained from the difference between the actual cost that patients get and the cost if adjustments are made. The total cost efficiency of the drug that can be saved in patients who require *adjustment* with inappropriate doses was IDR1,766,330 if dose adjustments are made. Ceftazidime for patients with renal impairment who have creatinine clearance between 6 – 15 ml/min was recommended at 500 mg every 24 hours. In the study, patients received ceftazidime 1 g every 8 hours and every 12 hours. The range of costs received by patients can be saved by IDR 42. 650 per day with adjustments. The use of cefixime in patients with renal impairment who have creatinine clearance values ≤ 20 ml/minute which was 200 mg every 24 hours. In 3 patients received 200 mg therapy every 12 hours. There was a dose adjustment for the use of cefixime reduced, from the use of cefixime 400 mg every day to the use of cefixime 200 mg per day. Costs borne in 1 day can be saved by IDR 6. 294. Ceftriaxone may be prescribed to patients with renal impairment at a dose of 1 g/12 hours. In 4 patients, ceftriaxone was prescribed 2 g / 12 hours. Ceftriaxone was a drug that does not require dose *adjustment* based on creatinine clearance values, but its use in patients with renal impairment was limited to 2 grams per day so in patients it was necessary to reduce the dose by 1 g per day and its use needs to be monitored. The cost of therapy received by patients can save IDR 9. 086 per day if dose adjustment was made. Excessive use of ceftriaxone in patients with renal impairment can increase toxicity to the kidneys, namely the occurrence of tubule necrosis[13].

Table 4. Cost difference that can be saved if dose adjustment was made

No.	Types of drugs	Real Cost	Adjustment Cost	Cost Difference
1	Antihiperurmia	IDR 3,750	IDR 1,800	IDR 1,950
2	Antibiotic	IDR 2,446,265	IDR 1,355,400	IDR 1,090,865
3	Analgesic	IDR 229,700	IDR 153,200	IDR 76,500
4	Antifibrinolithic	IDR 748,440	IDR 277,200	IDR 471,240
5	H_2 bloker	IDR 271,790	IDR 148,236	IDR 123,554
6	ACE Inhibitors	IDR 4,242	IDR 2,121	IDR 2,121
	Total	**IDR 3,704,187**	**IDR 1,937,957**	**IDR 1,766,230**

Discussion

In this study, it was found that the prevalence of men was greater than that of women. This can happen because men experience kidney damage faster than women and one of the influencing factors was the influence of hormones on kidney hemodynamics. In males, response to angiotensin II by maintaining GFR may lead to increased glomerular capillary pressure, whereas in females a decrease in GFR signifies no increase in glomerular capillary pressure. In global research, data were obtained from Thailand and Japan that the prevalence of CKD was lower in women than men. Most patients receiving kidney replacement treatment in the form of dialysis and kidney transplants were men with a 60:40 ratio of men to women [14.15] . The most comorbid concomitants in this study were hypertension, diabetes, and CHF. Hypertension can be a cause or result of CKD. In CKD, which was characterized by a decrease in GFR, it causes increased regulation of the renin-angiotensin-aldosterone system, causing fluid retention that can aggravate conditions[16–19]. About 1 in 3 adults with diabetes have CKD. Over time, high blood sugar due to diabetes can damage blood vessels in the kidneys and nephrons so that they do not function properly. Most patients with diabetes and CKD have a high risk of cardiovascular disease despite having undergone years of treatment[20] . Chronic Kidney Disease (CKD) patients accompanied by CHF are one of the leading causes of hospitalization, morbidity, and mortality. CHF can trigger and aggravate CKD through decreased renal blood flow, renal hemodynamic disorders, and due to ischemic[21,22.]

Dose appropriateness in CKD patients can increase treatment effectiveness and reduce treatment costs. To provide optimal treatment for CKD patients, knowledge of pharmacokinetic and pharmacodynamic changes in CKD was required. In addition, the identification of drugs that have the potential to cause nephrotoxicity and drug interactions was also important. The body's response to medication in CKD patients was highly variable, complex, and individualized. Dosing should be based on several factors, not only glomerular filtration rate but also other concomitant diseases, interactions with other drugs, and the patient's condition[23,24]. There were 56 types of drugs used by patients in this study that required dose adjustments. The class of drugs that require the most dose adjustment was antibiotics. The application of dosage recommendations in infectious diseases in CKD patients was limited by the lack and poor quality of available data. Dosing may refer to studies conducted under prescribing conditions that conform to dose-related infectious disease guidelines, indications, manner, and route of administration compared to pharmacokinetic, effectiveness, and tolerability parameters observed in patients with varying degrees of renal function. Dose adjustment was recommended for antimicrobials in patients with high renal clearance. The goal of antibiotic treatment in CKD patients is to achieve concentrations within the effective and non-toxic range of[25.26.]

Dose discrepancies in antibiotic use are still high. In this study, there were 14 instances of inappropriate doses in the use of antibiotics. Drug cost efficiency was obtained from the difference between the actual cost that patients get and the cost if *adjustments* are made. The total cost efficiency of the drug that can be saved in patients who require *adjustment* with inappropriate doses was IDR 1,766,330 if dose adjustments are made. The dose-adjustment intervention in this study resulted in savings in treatment costs the dose-adjustment intervention in this study resulted in savings in treatment costs. The drug costs that could be saved in this study represent a portion of the total possible savings that can be made. Savings in administrative costs, such as doctor fees, laboratory costs, and the cost of treatment in this study were not calculated. It can be concluded that dose adjustment intervention can save costs. Recommendations for medication dosage adjustments are part of the clinical pharmacist's daily responsibilities that need to be applied routinely. Indirectly, dose *adjustments* can improve the quality of life of patients. Close dose monitoring in patients with renal impairment can slow the progression of kidney damage to improve the patient's quality of life.

Conclusions

The appropriate dose in patients with CKD can improve the patient's clinical outcomes. There are savings in medical costs if dose adjustments are made when treating patients with CKD. Dose adjustment improves clinical outcome, effectiveness of therapy, and cost-effectiveness.

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Ethical Consideration

This research was conducted after obtaining ethical clearance approval with the number KE/FK/218/EC/2016.

Author Contribution

NDK, FR designed the study; NDK carried out the field work; NDK, FR analyzed the data; NDK, FR wrote the manuscript. All authors read and approved the final version of the manuscript

Competing Interests

In this research there were no funding sources involved in research planning, data collection, and analysis, writing articles.

Abbreviations

ACE : Angiotensin-converting enzyme
ADEs : Adverse drug events
CHF : Congestive heart failure
CKD : Chronic kidney disease
Clcr : Creatinine clearance
GFR : Glomerular filtration rate

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