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Study of Medicine Dosage Adjustments in Inpatients with Chronic Kidney Disease

Katharina Kening Weking[1]*, Liniati Geografi[1], Clara Ritawany Sinaga[1]
1. Program Studi S1 Farmasi, Sekolah Tinggi Ilmu Kesehatan Dirgahayu Samarinda, Indonesia

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Corresponding Author:
Katharina Kening Weking

Corresponding Author Email:
weking.kathy@gmail.com

ABSTRACT

Background: Decreased kidney function in patients with Chronic Kidney Disease (CKD) necessitates dose adjustment, especially for medicines that have a narrow therapeutic index to avoid unwanted medicine effects.

Objectives: The purpose of this study was to determine the medicine dosage adjustments in CKD patients and their therapy outcomes.

Methods: This type of research is descriptive with a retrospective approach. The sample in this study is the medical records of inpatient CKD patients at Abdoel Wahab Sjahranie Samarinda Hospital for the period May to November 2022. Calculation of GFR (Glomerular Filtration Rate) uses the MDRD (Modification of Diet in Renal Disease) formula.

Results: The results showed that the sex of most patients was male as many as 56.25%. The age of most patients in the range of 53-59 years old as many as 33.75%. Most CKD severity level is stage 5 as many as 91.25%. The most common comorbidities were hypertension (61 patients), diabetes mellitus (15 patients), and edema or pulmonary edema (11 patients). There were 77 patients requiring dose adjustment out of a total of 80 patients. There were 149 (34.89%) medicines requiring dose adjustment out of a total of 427 medicines, with the 5 most medicines being calcium carbonate (24.16%), furosemide (24.16%), metoclopramide (10.74%), paracetamol (10.74%), and ranitidine (7.39%). There were 128 (85.91%) medicines with doses appropriate to the Lexicomp 2023 or Renal Pharmacotherapy 2013. The therapy outcome improved in patients who required dose adjustments by 90.91%.

Conclusion: It is recommended to calculate GFR using a new formula such as eGFR using CKD-EPI, and collecting data with a larger number of samples.

Keywords: Chronic kidney disease; Dose adjustment; Glomerular filtration rate; Hospital

INTRODUCTION

According to WHO in 2018, 1/10 of the world's population is identified with Chronic Kidney Disease (CKD).[1] The incidence of CKD in Indonesia has increased from 2013 of 0.2% to 2018 of 0.38% of the total population in Indonesia.[2] The prevalence of CKD based on a doctor's diagnosis in residents aged ≥ 15 years in East Kalimantan Province is 0.42%.[3] In general, CKD is an abnormality in the structure or function of the kidneys that lasts for 3 months or more and is irreversible.[4] CKD classification is grouped based on cause, GFR (Glomerular Filtration Rate) category, and albuminuria category.[5] Most water-soluble medicines are excreted in certain amounts in intact form through the kidneys. Therefore, patients with reduced renal function require careful dose adjustment, especially for medicines that have a narrow therapeutic index.[6] Many medicines are largely eliminated by the kidneys, and even medicines with high rates of metabolism will likely require dose adjustments in CKD patients to maximize therapeutic results and minimize side effects. Most medicines that are unchanged in renal elimination can accumulate in CKD patients, which can further increase the risk of side effects.[4]

Research conducted at the Tegal Regency Hospital, Indonesia showed that of the 1,882 medicines prescribed, there were 338 (17.93%) medicines that required dose adjustments in CKD patients. Of these medicines, there were 175 (51.78%) medicines that had dosage adjustments made, and a total of 118 (67.43%) of these medicines resulted in improved therapy outcomes. CKD patients who received medicines with dose adjustments had medicine therapy outcomes achieved 1,992 times higher than CKD patients who received medicines without dose adjustments.[7] These results show a significant relationship between medicine dose adjustments and therapy outcomes in inpatient CKD patients. In another study conducted at Budhi Asih Regional Hospital, from 132 samples, results were obtained from 86 patients who received medication that required dose adjustment. From the 86 patients, there were 29 (33.72%) patients who received dose adjustments to the literature. Some medicines that require dose adjustments include Digoxin and Ranitidine. Digoxin is a medicine that is excreted approximately 50 - 70% in unchanged form through the kidneys and has a narrow therapeutic index with toxic levels > 3 µg/L. Meanwhile, around 30% of ranitidine at oral doses and 70% at intravenous doses is excreted in unchanged form through the kidneys. Both medicines have a prolonged elimination half-life in patients with kidney disease, so the possibility of toxicity increases. Therefore, dosage adjustments are needed to avoid these toxic effects.[8]

Abdoel Wahab Sjahranie Samarinda Regional General Hospital is a class A educational hospital that is one of the referral hospitals for CKD patients in East Kalimantan province and provides hemodialysis services. Based on the results of preliminary tests that have been carried out, there are 380 inpatient CKD patients in the period May to November 27th, 2022 at the hospital, with the most comorbidities in the form of hypertension and diabetes mellitus, the most complications in the form of anemia and pulmonary edema, and the most stages of CKD namely stage 5. Based on this background, researchers are interested in conducting research with the title "Study of Medicine Dosage Adjustments in Inpatients With Chronic Kidney Disease". This study aimed to determine medicine dose adjustments in CKD patients and their therapy outcomes.

METHODS

Study Design

This research is included in the type of descriptive research with a retrospective approach. Data collection in this study was carried out by collecting medical records of inpatient CKD patients at the Abdoel Wahab Sjahranie Samarinda Regional General Hospital for the period May to November 2022, to find out data on the patient's gender, age, comorbidities, laboratory test results in the form of serum creatinine level, type and dose of medication, and hospital discharge conditions. This research was conducted on March 13 until 31, 2023 in the medical records installation of the Abdoel Wahab Sjahranie Samarinda Regional General Hospital.

Population and Samples

The population in this study were inpatient Chronic Kidney Disease (CKD) patients for the period May to November 2022. The number of samples in this study was calculated using the following Slovin formula :

$$n = \frac{N}{1+Ne^2}$$

In sample calculations, the population of inpatient CKD patients in this study was 380 patients, with a tolerable allowance for inaccuracies due to a sampling error of 10%. The number of sample obtained in this study was 80 inpatient CKD patients in the period May to November 2022. The patients in this study were selected using non-random sampling with a purposive sampling technique. Inclusion criteria in this study included inpatient CKD patients aged ≥ 18 years, inpatient CKD patients with stages 4 and 5, inpatient CKD patients who had complete medical record data (gender, age, comorbidities, laboratory test results in the form of serum creatinine level, history of medicine use, medicine administration data in the form of type and dose of medicine, and therapy outcomes), and medical record data can be read properly. The exclusion criteria in this study was CKD patients who died during the period May to November 2022.

Study Instruments

The instruments used in this research consisted of patient data collection sheets, a laptop, a cell phone, stationery, a scientific calculator, the MDRD eGFR calculator in the Medscape® android application, Lexicomp online literature, and Renal Pharmacotherapy e-book. The sample used was medical records of inpatient CKD patients for the period May to November 2022 which were selected based on the inclusion criteria and exclusion criteria in this study.

Data Collection

Data collection was carried out using a purposive sampling technique. Patient identity data including gender, age, severity of CKD, comorbidities, serum creatinine, drug administration data, and therapy outcomes were taken from the patient's medical record. The data collection was carried out after obtaining a preliminary test permit and a research permit, both obtaining permits from the Program Studi S1 Farmasi Sekolah Tinggi Ilmu Kesehatan Dirgahayu Samarinda, and also obtaining permits at the Abdoel Wahab Sjahranie Samarinda Regional General Hospital.

Data Analysis

The data analysis technique used in this research was the univariate analysis technique. The univariate data consisted of patient gender, age, severity of CKD, comorbidities, number of patients requiring dose adjustments, type and number of medicines requiring dose adjustments, number of medicines with appropriate and inappropriate dose adjustments, and patient's therapy outcomes. Univariate data was presented in tabular form. The patient's GFR was calculated using the MDRD calculator (Modification of Diet in Renal Disease) 4 variables in the Medscape® android application.

RESULTS AND DISCUSSION

Characteristics of Chronic Kidney Disease (CKD) Patients

Gender

The gender characteristics of CKD patients in this study can be seen in Table I which were dominated by male patients as many as 45 (56.25%) patients, while female patients were 35 (43.75%) patients. These results are in line with previous research conducted at Budhi Asih Regional Hospital which stated that men suffer from CKD more often than women because men have different lifestyles from women, including smoking and consuming energy drinks.[8]

Cigarettes contain more than 100 types of cigarettes toxic substances, which have been proven to be carcinogenic, hepatotoxic, immunosuppressive, and nephrotoxic to the body. Nicotine is one of the ingredients in cigarettes that is nephrotoxic. Nicotine increases blood pressure and heart rate. In this case, nicotine also plays an important role as an intermediary for kidney damage, because increasing blood pressure is one of the most important factors in increasing the progression of CKD.[9] Blood pressure will cause the blood vessels in the kidneys to become compressed, causing problems with blood vessels in the kidneys, resulting in decreased kidney function.[10] Another lifestyle is consuming energy drinks, which contain a combination of caffeine and taurine which works as a stimulant. The mechanism of this energy drink is activation of the sympathetic nerves which will result in an acceleration of the heart rate to pump blood and oxygen, as well as vasoconstriction of blood vessels, resulting in an increasing blood pressure (hypertension). Renal function will also decrease and the end products of protein metabolism which are normally excreted in the urine will accumulate in the blood, and the symptoms will become more severe for the patient.[11]

Age

The age characteristics of CKD patients in this study can be seen in Table I which were mostly in the age range of 53 to 59 years old with 27 (33.75%) patients and the age range of 39 to 45 years old with 16 (20%) patients. These results are in line with previous research conducted at Budhi Asih Regional Hospital, where CKD patients were dominated by patients aged 40 years old and over to under 65 years old.[8] This can happen because after the age of 30 years old, every decade (10 years), the kidneys will experience atrophy (tissue damage) and the thickness of the renal cortex will decrease by around 20% of its normal thickness.[12] Physiologically, as age increases, kidney function can also decrease which then increases the risk factors for hypertension or even obesity.[13] In addition, nephron damage to the kidneys also increases with age.[14] These non-functioning nephrons then suppress normally functioning nephrons, which naturally causes a decrease in renal perfusion pressure and a decrease in the Glomerular Filtration Rate (GFR).[4]

CKD Severity Level

The severity characteristics of CKD patients in this study can be seen in Table I which were dominated by CKD stage 5 patients with 73 (91.25%) patients, while stage 4 patients with 7 (8.75%) patients. These results are in line with research conducted at the Tegal Regency Hospital, where the majority of CKD patients were at stage 5 with 166 (83%) patients.[7] The number of hospitalized CKD patients is greater at stage 5 because patients only

Table I. Characteristics of CKD Patients

Characteristics		Number of Patients	Percentage (%)
Gender	Man	45	56.25
	Woman	35	43.75
Total		80	100
Age Range (Years)	18 - 24	1	1.25
	25 - 31	5	6.25
	32 - 38	5	6.25
	39 - 45	16	20
	46 - 52	12	15
	53 - 59	27	33.75
	≥ 60	14	17.5
Total		80	100
Severity Level	4	7	8.75
(Stage) of CKD	5	73	91.25
Total		80	100
Comorbidities	Hypertension	61	76.25
	Diabetes Mellitus	15	18.75
	Edema / Pulmonary Edema	11	13.75
	Gout	4	5
	Atherosclerosis	3	3.75
	Heart Failure	3	3.75
	Cholesterol (Hyperlipidemia)	2	2.5
	Pneumonia	2	2.5
	Coronary Heart	1	1.25

experience symptoms (such as fatigue, nausea, vomiting, loss of appetite, and other symptoms) when the patient is already at stages 4 and 5 of CKD. Meanwhile, at lighter stages, such as in stages 1, 2, and 3, the patient is not yet aware of the condition of decreased kidney function that he is experiencing because he has not felt the symptoms, so, at the same time, the patient has not had an examination or treatment at the hospital.[15] In patients with CKD stage 4, the patient's Glomerular Filtration Rate (GFR) is in the range of 15 - 29 mL/minute/1.73 m^2, while in patients with CKD stage 5, the patient's GFR is < 15 mL/minute/1.73 m^2.[16]

Comorbidities

The characteristics of the comorbidities of CKD patients in this study can be seen in Table I which were dominated by hypertension in 61 (76.25%) patients, diabetes mellitus in 15 (18.75%) patients, and edema or pulmonary edema in 11 (13.75%) patients. These results are in line with research conducted at Budhi Asih Regional Hospital, where there are several comorbidities with the highest number of CKD patients, including diabetes mellitus with 40 (30.30%) patients, and hypertension with 39 (29.54%) patients.[8]

Hypertension and diabetes mellitus can cause or worsen CKD. In patients with hypertension, high blood pressure will cause the blood vessels in the kidneys to become compressed, so that the flow of food substances to the kidneys becomes disrupted, which can cause the blood vessels to become damaged and kidney function to decrease, thus causing kidney function failure. In patients with diabetes mellitus, blood sugar levels that are too high will make the kidneys have to work harder than normal in filtering the blood. This can result in kidney leaks if the kidneys work too hard in filtering the blood continuously.[10]

Comorbidities in the form of edema can also occur in CKD patients. Initially, there is a leak of albumin protein which is excreted in the urine, where protein is one of the components needed by the body, so it should remain stored in the body and not be excreted in large quantities through the urine. This condition then develops and results in a decrease in the filtering function of the kidneys. At the same time, there is a buildup of a lot of waste or waste from waste substances in the body due to a decrease in the filtering function of the kidneys, which is indicated by edema or swelling in the body.[10] CKD patients in this study also experienced pulmonary

edema which was the result of a combination of excess fluid buildup (edema) and abnormal permeability in the pulmonary microcirculation, as well as high intravascular pressure or increased capillary membrane permeability which resulted in rapid fluid extravasation, resulting in impaired air exchange in the alveoli is progressive and results in hypoxia or the absence of enough oxygen in the tissues to maintain body functions.[17]

Number of Inpatients with CKD Requiring Dosage Adjustments

Patients who do or do not require dose adjustments in the medicines used are known by comparing the types of medicines received by the patient with the types of medicines listed in the literature used in this study. The patient is stated to require a dose adjustment if in the literature, the medicine received by the patient has a statement that requires a dose adjustment in patients with CKD, conversely, the patient is stated not to require a dose adjustment, if there is not a single medicine that has a statement that requires a dose adjustment in the patient with CKD in the literature. The literature used in this research consists of 2 pieces of literature, namely Lexicomp online literature used for 327 (76.58%) medicines, and Renal Pharmacotherapy e-book used for 100 (23.42%) medicines. Based on Table II, inpatient CKD patients who required dose adjustments were 77 (96.25%) patients, while there are 3 (3.75%) patients who did not require dose adjustments.

Generally, medicines are excreted in certain amounts in intact form through the kidneys. In CKD patients, there is a decrease in GFR (Glomerular Filtration Rate) which causes a decrease in the ability to excrete medicines through the kidneys, resulting in a longer medicine elimination time. Therefore, it is necessary to adjust the medicine dose, especially for medicines that have a narrow therapeutic window. This is done to prevent the buildup of medicine levels or medicine toxicity in the patient's body.[6]

Types and Number of Medicines Requiring Dosage Adjustments in Inpatient CKD Patients

Based on Table III, of a total of 427 medicines, there are 149 (34.89%) medicines that required dose adjustments in patients with CKD, and 278 (65.11%) medicines that did not require dose adjustments in patients with CKD. Medicines that require or do not require dose adjustments are known by comparing the types of medicines received by the patient with the types of medicines listed in the literature. A medicine is stated to require dose adjustment, if in the literature, the medicine has a statement requiring dose adjustment in patients with CKD, conversely, a medicine is stated to not require dose adjustment, if in the literature, the medicine does not have a statement requiring dose adjustment in patients with CKD. Based on Table IV, of the 149 medicines that require dose adjustments, 5 types of medicines dominate. These five types of medicines include calcium carbonate as many as 36 (24.16%) medicines, furosemide as many as 36 (24.16%) medicines, metoclopramide as many as 16 (10.74%) medicines, paracetamol as many as 16 (10.74%) medicines, and ranitidine as many as 11 (7.39%) medicines.

Calcium carbonate is a phosphate binder that is often given to patients with CKD. In CKD patients, phosphate binders are used to keep phosphate levels normal, to prevent disease progression Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) due to the kidney's inability to filter blood and regulate hormones and minerals.[18] Calcium carbonate needs to be used in the right dose and not excessively in CKD patients because it has the potential to cause hypercalciuria. Hypercalciuria is the cause of the formation of calcium stones in the kidneys. Although most cases of kidney calcium stones are caused by hyperparathyroid disease, in patients who have CKD, calcium supplements must also be given in adequate doses.[19]

Furosemide is a loop diuretic. In CKD patients, furosemide is used to reduce fluid accumulation or edema, as well as a therapy for hypertension, where both diseases are included in the comorbidities commonly experienced by CKD patients. Loop diuretic like furosemide is highly protein-bound to albumin and acidic. Thus, these types of medicines are secreted and not filtered or diffused passively into the proximal tubule by organic acid transporters into the tubular lumen, where they act by blocking the Na/K/2Cl counterporter in the thick ascending loop of Henle, where 20 - 25% Sodium filtered through the glomerulus is reabsorbed.[20] In CKD, organic anions accumulate and compete with diuretics for organic acid transporter receptor sites.[21] Consequently, higher doses are required to overcome competitive inhibition and achieve therapeutic urine concentrations in patients with CKD.[22]

Metoclopramide is a medicine used to relieve several health problems in the stomach and intestines, such as symptoms of nausea and vomiting. In CKD patients, symptoms of nausea and vomiting can be caused by a buildup of waste or metabolic waste that accumulates in the blood, which cannot be removed by the kidneys due to decreased kidney function. Metoclopramide is also one of the medicines that requires dose adjustment in CKD patients. This is because, in patients with impaired kidney function, clearance of metoclopramide is

Table II. Number of Inpatient CKD Patients who Require and Do Not Require Dose Adjustment

Patient Category	Number of Patients	Percentage (%)
Patients who require dose adjustment	77	96.25
Patients who do not require dose adjustment	3	3.75
Total	80	100

Table III. Number of Medicines that Require and Did Not Require Dose Adjustment

Type of Medicine	Number of Medicine	Percentage (%)
Medicines that require dose adjustment	149	34.89
Medicines that do not require dose adjustment	278	65.11
Total	427	100

Table IV. Type and Number of Medicines that Require Dose Adjustment

Type of Medicine Require Dose Adjustment	Number of Medicine	Percentage (%)
Calcium Carbonate	36	24.16
Furosemide	36	24.16
Metoclopramide	16	10.74
Paracetamol	16	10.74
Ranitidine	11	7.39
Allopurinol	6	4.03
Bisoprolol	6	4.03
Cefixime	5	3.36
Potassium Chloride	3	2.01
Ramipril	3	2.01
Cetirizine	2	1.34
Clonidine	2	1.34
Digoxin	2	1.34
Amoxicillin	1	0.67
Tranexamic Acid	1	0.67
Azathioprine	1	0.67
Captopril	1	0.67
Tramadol	1	0.67
Total	149	100

reduced by 70%. In addition, the plasma elimination half-life of this medicine also increases by around 10 - 15 hours in patients with impaired renal function.[23]

Paracetamol is an analgesic that is also used in CKD patients, one of which is to treat low back pain. Low back pain that occurs around the waist and lumbar (lower backbone) can be caused by problems with the kidney itself. Paracetamol is an analgesic that requires dose adjustment for CKD patients. This is because less than 5% paracetamol is excreted in unchanged form. Paracetamol undergoes metabolism which produces a minor metabolite, but it is very active and important at large doses, namely NAPQI which is toxic to the liver and kidneys. At levels that cause toxicity or liver disease, the half-life will double or more. This is what makes use of paracetamol should be considered in CKD patients.[24] The most likely mechanism for the potential risk is increased severity of kidney disorders associated with the use of paracetamol is acute tubular necrosis (a kidney lesion characterized by destruction and necrosis of tubular epithelial cells and an acute decrease in kidney function). About 5% of paracetamol is metabolized via phase I metabolism (cytochrome P-450 pathway) to form Nacetyl-p-benzoquinone imine. The cytochrome P-450 pathway can be detected in both the kidney and liver, although

Table V. Number of Medicines Received by Inpatient CKD Patients

Number of Medicine	Number of Patients	Percentage (%)
5	16	20
4	16	20
3	13	16.25
7	11	13.75
6	10	12.5
8	5	6.25
2	3	3.75
11	3	3.75
9	1	1.25
10	1	1.25
12	1	1.25
Total	80	100

both are quite variable in each organ. This process produces lipid peroxides that lead to cell apoptosis and initiate programmed cell death. For this reason, tissue necrosis and organ dysfunction may occur.[25]

Ranitidine is one of the medicines used for symptoms or diseases related to stomach acid. In CKD patients, stomach acid is prone to increase, because decreased kidney function results in an increases product that should be excreted by the kidneys, one of which is gastrin which is a hormone that can stimulate gastric acid secretion.[26] Ranitidine also requires dose adjustments in CKD patients because ranitidine is excreted by the kidneys in unchanged form approximately 30% for oral doses and 70% for intravenous doses. Ranitidine experienced a prolonged elimination half-life in CKD patients. Prolonged elimination half-life of ranitidine will be proportional to the level of kidney damage which is described by the Glomerular Filtration Rate (GFR). Therefore, it is recommended to reduce or adjust the medicine dose of ranitidine in CKD patients.[27]

Dosage Appropriateness of Medicines that Require Dosage Adjustment in Inpatient CKD Patients

The appropriateness of medicine doses is assessed according to the appropriateness of medicine doses received by inpatient CKD patients with medicine doses in the Lexicomp or Renal Pharmacotherapy literature based on the patient's GFR. Based on Table VI, of the 18 types of medicines with a total of 149 medicines that required dose adjustments, there were 15 types of medicines with a total of 128 (85.91%) medicines with doses that were appropriate to the literature. There were 8 types of medicines with doses that were not appropriate to the literature, with a total of 21 (14.09%) medicines. Of the 128 medicines with appropriate doses, 4 types of medicines dominate, including calcium carbonate as many as 36 (28.13%) medicines, furosemide as many as 36 (28.13%) medicines, paracetamol as many as 16 (12.50%) medicines, and metoclopramide as many as 10 (7.81%) medicines. Of the 21 medicines with inappropriate doses, 4 types of medicines dominate, including ranitidine as many as 7 (33.33%) medicines, metoclopramide as many as 6 (28.57%) medicines, allopurinol as many as 2 (9.53%) medicines, and bisoprolol as many as 2 (9.53%) medicines.

Based on Table VII, calcium carbonate is the first most common medicine among 128 medicines whose dosage is appropriate with the literature. Calcium carbonate has a normal dose of 1.5 - 4 grams/day. Based on the Lexicomp, calcium carbonate in CKD patients with GFR < 60 mL/minute/1.73 m^2 is recommended to adjust the dose not to exceed 2,000 mg/day. In this study, CKD patients with GFR < 60 mL/minute/1.73 m^2, received a dose of 500 mg 2 - 3 times a day, where this dose is appropriate with the dose in the Lexicomp.

Based on Table VII, furosemide is the second most common medicine whose dosage is appropriate with the literature. Furosemide has a normal dose of 20 mg/day. Based on the Lexicomp, furosemide in CKD patients with GFR < 30 mL/minute/1.73m^2 is recommended to adjust the dose not to exceed 160 - 200 mg, whereas in furosemide continuous intravenous infusion, an initial dose of 20 mg/hour is recommended. In this study, CKD patients with GFR < 30 mL/minute/1.73 m^2, received an oral dose of 40 mg 2 - 3 times a day, an intravenous injection dose of 20 mg 2 - 3 times a day, 1 - 2 ampoules, and a dose of continuous intravenous infusion of 20 mg/hour, where all of these three doses are appropriate with the doses in the Lexicomp.

Based on Table VII, paracetamol (acetaminophen) is the third most common medicine whose dosage is appropriate with the literature. Paracetamol has a normal dose of 500 - 1,000 mg every 4 - 6 hours. Based on the

Table VI. Number of Medicines with Appropriate and Inappropriate Doses According to The Lexicomp or Renal Pharmacotherapy Literature

Type of Medicine	Number of Medicine	Percentage (%)
Medicines with doses that appropriate to the literature	128	85.91
Medicines with doses that are not appropriate to the literature	21	14.09
Total	149	100

Table VII. Type and Number of Medicines with Appropriate Doses According to The Lexicomp or Renal Pharmacotherapy Literature

Type of Medicine	Number of Medicine	Percentage (%)
Calcium carbonate	36	28.13
Furosemide	36	28.13
Paracetamol	16	12.50
Metoclopramide	10	7.81
Cefixime	5	3.90
Allopurinol	4	3.13
Bisoprolol	4	3.13
Ranitidine	4	3.13
Potassium Chloride	3	2.34
Ramipril	3	2.34
Clonidine	2	1.56
Digoxin	2	1.56
Tranexamic Acid	1	0.78
Cetirizine	1	0.78
Tramadol	1	0.78
Total	128	100

Renal Pharmacotherapy, paracetamol in CKD patients with GFR > 50 mL/minute/1.73 m^2 is recommended to adjust the dose to a maximum of 650 mg every 6 hours for oral preparations, and 1,000 mg every 6 hours for intravenous preparations. In CKD patients with GFR 10 - 50 mL/minute/1.73m^2, itis recommended to adjust the dose to a maximum of 650 mg every 6 hours in oral preparations, and a maximum of 1,000 mg every 6 hours in intravenous injection preparations, whereas in CKD patients with GFR < 10 mL/minute/1.73m^2, it is recommended to adjust the dose to a maximum of 650 mg every 8 hours in the oral preparation, and 1,000 mg every 8 hours in the intravenous preparation. In this study, CKD patients with a GFR of 10 - 50 mL/minute/1.73 m^2, receive a dose of 500 mg 4 times a day in an oral preparation, a dose of 1 gram 4 times a day, and a dose of 500 mg 4 times a day in an intravenous injection preparation. In CKD patients with GFR < 10 mL/minute/1.73 m^2, paracetamol is given at a dose of 500 mg 3 times a day in oral preparations, and a dose of 1 gram 3 times a day in intravenous injection preparations. These five doses are appropriate with the doses in the Renal Pharmacotherapy.

Based on Table VII, metoclopramide is the fourth most common medicine whose dosage is appropriate with the literature. Metoclopramide has a normal dose of 10 or 20 mg, 1 time per day. Based on the Renal Pharmacotherapy, metoclopramide in CKD patients with GFR > 50 mL/minute/1.73 m^2 is recommended to adjust the dose to 10 mg 4 times a day. In CKD patients with GFR < 10 mL/minute/1.73m^2, it is recommended to adjust the dose to 5 mg a maximum of 4 times a day, while in CKD patients with GFR 10 - 50 mL/minute/1.73m^2, it is recommended to adjust the dose to 7.5 mg maximum 4 times a day. In this study, CKD patients with GFR < 10 mL/minute/1.73 m^2, received a dose of 5 mg once a day, whereas in CKD patients with GFR 10 - 50 mL/minute/1.73 m^2, metoclopramide is given at a dose of 7.5 mg 1 - 3 times a day. Both doses are appropriate with the doses in the Renal Pharmacotherapy.

Based on Table VIII, ranitidine is the first most common medicine among 21 medicines whose dosage is inappropriate with the literature. Ranitidine has a normal dose of 50 mg every 6 - 8 hours (3 - 4 times a day).

Table VIII. Type and Number of Medicines with Inappropriate Doses According to The Lexicomp or Renal Pharmacotherapy Literature

Type of Medicine	Number of Medicine	Percentage (%)
Ranitidine	7	33.33
Metoclopramide	6	28.57
Allopurinol	2	9.53
Bisoprolol	2	9.53
Amoxicillin	1	4.76
Azathioprine	1	4.76
Captopril	1	4.76
Cetirizine	1	4.76
Total	21	100

Based on the Renal Pharmacotherapy, ranitidine in CKD patients with GFR > 50 mL/minute/1.73 m^2 is recommended to adjust the dose to 50 mg every 8 hours, while in CKD patients with GFR 10 - 50 mL/minute/1.73 m^2, it is recommended to adjust the dose to 50 mg every 12 hours. In CKD patients with GFR < 10 mL/minute/1.73 m^2, it is recommended to adjust the dose to 50 mg every 24 hours (1 time per day). In this study, there were CKD patients with GFR < 10 mL/minute/1.73 m^2 who received the ranitidine 50 mg 2 times a day, where this dose is inappropriate with the dose in the Renal Pharmacotherapy.

Based on Table VIII, metoclopramide is the second most common medicine whose dosage is inappropriate with the literature. Metoclopramide has a normal dose of 10 or 20 mg, once a day. Based on the Renal Pharmacotherapy, metoclopramide in CKD patients with GFR > 50 mL/minute/1.73 m^2 is recommended to adjust the dose to 10 mg 4 times a day, while in CKD patients with GFR 10 - 50 mL/minute/1.73 m^2, it is recommended to adjust the dose to 7.5 mg 4 times a day. In CKD patients with GFR < 10 mL/minute/1.73 m^2, it is recommended to adjust the dose to 5 mg a maximum of 4 times a day. In this study, there were CKD patients with GFR < 10 mL/minute/1.73 m^2 who received the metoclopramide 10 mg 3 times a day, where this dose is inappropriate with the dose in the Renal Pharmacotherapy.

Based on Table VIII, allopurinol is the third most common medicine whose dosage is inappropriate with the literature. Allopurinol has a normal dose of 600 - 800 mg/day. Based on the Renal Pharmacotherapy, allopurinol in CKD patients with GFR > 50 mL/minute/1.73 m^2 is recommended to adjust the dose to 200 mg once a day, while in CKD patients with GFR < 10 mL/minute/1.73 m^2, it is recommended to adjust the dose to 100 mg once a day. In CKD patients with GFR 10 - 50 mL/minute/1.73 m^2, it is recommended to adjust the dose to a maximum of 150 mg once a day. In this study, there were CKD patients with GFR 10 - 50 mL/minute/1.73 m^2 who received a dose of allopurinol 300 mg once a day, where this dose is inappropriate with the dose in the Renal Pharmacotherapy.

Based on Table VIII, bisoprolol is the fourth most common medicine whose dosage is inappropriate with the literature. Bisoprolol has a normal dose of 5 - 10 mg, a maximum of 20 mg, once a day. Based on the Renal Pharmacotherapy, bisoprolol in CKD patients with GFR > 50 mL/minute/1.73 m^2 is recommended to adjust the dose to 5 mg every 24 hours, while in CKD patients with GFR 10 - 50 mL/ minute/1.73 m^2, it is recommended to adjust the dose to 2.5 - 5 mg every 24 hours. In CKD patients with GFR < 10 mL/minute/1.73 m^2, it is recommended to adjust the dose to 2.5 mg every 24 hours (1 time per day). In this study, there were CKD patients with GFR < 10 mL/minute/1.73 m^2 who received a dose of bisoprolol 5 mg once a day, where this dose is inappropriate with the dose in the Renal Pharmacotherapy. The inappropriate of medicine doses received by inpatient CKD patients with the Lexicomp and Renal Pharmacotherapy literature can be caused by considerations from medical personnel who treat patients, regarding to the therapeutic needs of each inpatient CKD patients.[8]

Therapy Outcomes in Inpatient CKD Patients who Require Dosage Adjustments

Based on Table IX, of the 77 inpatients with CKD who required dose adjustments, there are 70 patients were discharged from the hospital with improved therapy outcomes, and 7 patients were discharged from the hospital with unimproved therapy outcomes. Of the 3 inpatients with CKD who did not require dose adjustments, there are 2 patients were discharged from the hospital with improved therapy outcomes, and 1 other patient was discharged from the hospital with unimproved therapy outcomes. Therapy outcomes in patients who require medicine dose adjustments and therapy outcomes in patients who do not require medicine dose adjustments

Table IX. Therapy Outcomes in CKD Patients who Require Dosage Adjustment

Therapy Outcomes in CKD Patients who Require Dosage Adjustment	Number of Patients	Percentage (%)
Improved	70	90.91
Not Improved	7	9.09
Total	77	100

Table X. Therapy Outcomes and Appropriateness of Medicine Doses in CKD Patients

Therapy Outcome / Dosage Appropriateness	Improved	Not Improved
Dosage Adjustment Appropriate with The Literature	121 medicines	7 medicines
Dosage Adjustment Inappropriate with The Literature	14 medicines	7 medicines

are known by looking at vital signs (such as body temperature, pulse, respiratory rate, and blood pressure), laboratory results (serum creatinine level) and information about the condition of being discharge from the hospital. Normal body temperature is in the range of 36.5 - 37.2°C, normal pulse is in the range of 60 - 100 times per minute, normal respiratory frequency is in the range of 95 - 100%, normal blood pressure is in the range of < 120/80 mmHg, and normal serum creatinine is in the range of 0.6 - 1.3 mg/dL. The therapy outcome is said to have improved if there is improvement in vital signs, laboratory result, and information about the condition of being discharged from the hospital, while the therapy outcome is said to have not improved if there is no improvement in vital signs, laboratory result, and information about the condition of discharge from the hospital.[7] The limitations of this study are that a newer GFR calculation formula has not been used, and the sample size is not large enough to provide a broader picture of dose adjustments in hospitalized CKD patients.

CONCLUSION

The majority of hospitalized CKD (Chronic Kidney Disease) patients are men. Most patients are in the age range of 53 - 59 years. The severity of CKD is highest at stage 5. The most common comorbidity is hypertension. The number of patients who required dose adjustments was 77 (96.25%) patients. The number of medicines requiring dose adjustment was 149 (34.89%) medicines. There were 128 (85.91%) medicines with doses appropriate to the literature, while there were 21 (14.09%) medicines with doses inappropriate to the literature. Therapy outcomes improved in 70 (90.91%) patients who required dose adjustments, and did not improve in 7 (9.09%) patients who required dose adjustments. It is recommended to use a new formula such as eGFR using CKD-EPI when calculating a patient's GFR, and collecting data with a larger number of samples.

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STATEMENT OF ETHICS

This research was declared to have passed ethical review by the Health Research Ethics Committee of Abdoel Wahab Sjahranie Samarinda Regional General Hospital (24/KEPK-AWS/III/2023) on March 3, 2023.

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