Jurnal Ilmiah Farmako Bahari
Journal Homepage : https://journal.uniga.ac.id/index.php/JFB

STUDY OF DOSAGE ADJUSTMENT OF ORAL ANTIDIABETIC DRUG IN TYPE II DIABETES MELLITUS PATIENTS WITH DISORDERS KIDNEY FUNCTION AT DR. SOEKARDJO TASIKMALAYA HOSPITAL

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ARTICLE HISTORY

Received: 8 November 2022 | Revised: 19 January 2023 | Accepted: 26 January 2023

Abstract

Diabetic nephropathy is one of the complications in DM that can end up becoming DM kidney failure. Nephropathy complications, if not handled properly, will lead to terminal chronic kidney disease. One of the factors that trigger complications of diabetic nephropathy in DM patients is the long-term use of oral anti-diabetic drugs. Therefore, proper dosage adjustment of these antidiabetic drugs, which are excreted through the kidneys, is required. The purpose of this study was to determine whether the dose received by type II DM patients with impaired renal function in the hospital was appropriate or not. This research will be carried out quantitatively and retrospectively by collecting patient medical record data at the hospital, and then the data obtained will be analyzed descriptively by calculating the creatinine clearance using the Cockcroft & Gault formula and comparing it with the literature dose based on the value of creatinine clearance. The sampling technique used was purposive sampling using the inclusion and exclusion criteria determined by the researcher. The inclusion criteria are data on type II diabetes mellitus patients with impaired kidney function at dr. Soekardjo Tasikmalaya Hospital in October–December 2020 who were treated with oral anti-diabetic drugs. The exclusion criteria were type II DM patients with impaired renal function who were treated with insulin, type I DM patients, and type II DM patients with impaired renal function who were treated with oral antidiabetic with incomplete laboratory data. Based on research that has been conducted on 35 samples, as many as 25 people, or 71.43 percent of patients, received therapeutic doses that were not in accordance with their kidney conditions. Meanwhile, 10 people, or 28,57% of patients, received a therapeutic dose according to their kidney condition.

Key words: diabetic nephropathy, dosage adjustment, kidney disorders, oral antidiabetic, type II diabetes mellitus

Introduction

The International Diabetes Federation (IDF) estimates the number of diabetics in a population of 20-79 years old in several countries around the world in 2019 and has identified the ten countries with the highest number of sufferers.China, India, and the

ISSN:2087-0337
E-ISSN:2715-9949

United States rank in the top three with 116.4 million, 77 million, and 31 million sufferers, respectively. Indonesia itself is in 7th place with 10.7 million sufferers and is the only country in Southeast Asia on the list. Based on the results of the Riset Kesehatan Dasar (Riskesdas) in 2018, the prevalence of diabetes mellitus based on a doctor's diagnosis in the population of all ages by province reached 1.5% of a total of 34 provinces, with DKI Jakarta province having the highest prevalence of DM (2.6%). Meanwhile, based on the characteristics of the residence of urban residents, the DM prevalence was higher (1.89%) than that of rural residents (1.01%).[1,2]

DM disease that is not treated quickly and appropriately can worsen the hyperglycemia suffered by the patient, resulting in complications that cause damage to various systems in the body. Diabetes mellitus is one of the factors that can cause heart disease, stroke, retinopathy, neuropathy, and nephropathy (kidney failure).[3]

Diabetic nephropathy is one of the complications of DM that can end up in kidney failure. Nephropathy is the cause of death in DM. In Asia, nearly 60% of diabetics have diabetic nephropathy. There are 25% of patients with kidney failure undergoing dialysis therapy who have DM, especially Type II DM (T2DM). [4] DM with complications of nephropathy, if not treated properly, will lead to terminal chronic kidney disease.[7] One of the factors that trigger complications of diabetic nephropathy in DM patients is the long-term use of oral anti-diabetic drugs. This happens because these oral antidiabetic drugs will be excreted through the kidneys, and if the doses taken are not appropriate, they will cause toxic effects that will worsen kidney disorders. [1] Therefore, proper dosage adjustment of these antidiabetic drugs, which are excreted through the kidneys, is required.[5]

Patients with impaired renal function require doses of drugs that are under their creatinine clearance (CrCl) to achieve the expected therapeutic effect and prevent the progression of impaired renal function. Because if the dose is not appropriate or exceeds the dose that should be, it will lead to the possibility of drug accumulation in the blood. In addition, the administration of excessive doses of drugs can cause blood sugar levels in the body to drop dramatically because the drug concentration in the blood exceeds the therapeutic level of the drug, which will cause serious hypoglycemia.[6]

Based on the background of the problem above, the purpose of this study was to determine the appropriateness of the dose received by T2DM patients with impaired renal function in the hospital. The benefits of this paper are for the authors to add insight into the importance of dose adjustment for patients who have impaired kidney function, besides the benefits of this writing for hospitals as a consideration in therapeutic management, especially for type II DM patients who have impaired kidney function.

Method

The study was conducted in a descriptive and retrospective manner by collecting patient medical record data at the hospital, including the completeness of patient data such as age, gender, weight, disease diagnosis, oral antidiabetic drugs used, doses used, dosage regimens, and laboratory examination data in the form of examination results. blood sugar, creatinine, and blood urea. Then the data obtained were analyzed descriptively by calculating the creatinine clearance using the Cockcroft and Gault formula. Then the drug dose received by the patient at the hospital was compared with the literature dose based on the value of creatinine clearance to see whether the dose given was appropriate or not. The sampling technique used is purposive sampling using inclusion and exclusion criteria selected by the researcher. The inclusion criteria are data on type II diabetes mellitus patients with impaired kidney function at dr. Soekardjo Tasikmalaya Hospital in October–December 2020 who were treated with oral anti-diabetic drugs. The exclusion criteria were type II DM patients with impaired renal function who were treated with insulin, type I DM patients, and type II DM patients with

ISSN:2087-0337
E-ISSN:2715-9949

impaired renal function who were treated with oral antidiabetic with incomplete laboratory data.

This research has obtained research permission from Kesbangpol Tasikmalaya with number 070/187/KESBANGPOL and a research permit from RSUD dr. Soekardjo Tasikmalaya with number 420/1275/Diklat/2021.

Result

According to the research, the data on tT2DM patients with impaired kidney function in the study conducted in October-December 2020 was 130 people, with a sample of up to 35 people meeting the inclusion and exclusion criteria. Patients take biguanides (Metformin), sulfonylurea drugs (Glimepirid, Glibenclamide), and -glucosidase inhibitors (Acarbose) orally, either alone or in combination.

Table 1. Patient Demographic Data and Oral Antidiabetic Used

Category	Quantity (n=35)	Percentage (%)
Gender		
Male	10	29
Female	25	71
Age (years)		
36-45	6	17
46-55	7	20
56-65	14	40
>65	8	23
Oral Antidiabetic Therapy Used		
Acarbose (single)	1	3
Glimepiride (single)	6	17
Metformin (single)	16	46
Acarbose-Glimepiride (combination)	1	3
Acarbose-Glibenclamide (combination)	1	3
Glimepiride-Metformin (combination)	6	17
Acarbose-Glimepiride-Metformin (combination)	4	11

Table 2. Creatinine Clearance Value Group (CrCl)

No	Group	Stage of Kidney Injury	CrCl (mL/minutes)	Quantity (person)	Percentage (%)
1	Stage 1	Normal	>80	0	0
2	Stage 2	Mild	50-80	5	14,29
3	Stage 3	Moderate	30-50	11	31,43

ISSN:2087-0337
E-ISSN:2715-9949

Table 2. (Extension)

No	Group	Stage of Kidney Injury	CrCl (mL/minutes)	Quantity (person)	Percentage (%)
4	Stage 4	Severe	=30	13	37,14
5	Stage 5	End-stage	=15	6	17,14
	Total			35	100

Table 3. Oral Antidiabetic Dosage in Normal Conditions and Based on Creatinine Clearance Values (CrCl) [7,8]

No	Drugs	Normal Dosage (mg)	Dosage based on CrCl	
			CrCl (mL/min)	Literature Dosage
1	Acarbose	25	>50	50 mg
			10 -50	Not recommended
			<10	Not recommended
2	Glibenclamide	5	20-50	1,25 mg – 2,5 mg
			10-20	1,25 mg – 2,5 mg
			<10	1,25 mg – 2,5 mg with continuous monitoring
3	Glimepiride	1 – 4	20-50	Recommend dosage
			10-20	1 mg
			<10	1 mg
4	Metformin	500	40-50	250 mg – 750 mg
			10-40	25% recommend dosage
			<10	Not recommended

ISSN:2087-0337
E-ISSN:2715-9949

Table 4. Dosage Suitability of Oral Antidiabetic Types

No.	Oral Antidiabetic	Suitable	Not Suitable
1	Acarbose	0	7
2	Glibenclamide	0	1
3	Glimepiride	10	7
4	Metformin	5	21

*PS: 1 patient can receive more than 1 drug

Table 5. Percentage of Dosage Suitability

No.	Suitability	Quantity (person)	Percentage (%)
1	S (Suitable)	10	28,57
2	NS (Not suitable)	25	71,43
	Total	35	100

Discussion

In Table 1, it can be seen that the demographic data of type 2 DM patients with impaired kidney function based on gender have the highest percentage of women (71%). The higher incidence of diabetes mellitus in women can be caused by differences in body composition and differences in sex hormone levels between women and men. Women have more fat tissue than men. This can be seen from the difference in normal fat levels between adult men and women, where in men it ranges from 15-20% while in women it ranges from 20-25% of body weight. The decrease in the concentration of the hormone estrogen in postmenopausal women can also cause an increase in body fat reserves, especially in the abdominal area, which will increase the release of free fatty acids. Both of these conditions can cause insulin resistance, which occurs in diabetes mellitus.[9] In the age category, the group with the highest percentage is 56–65 years old (late elderly), at 40%. Risk factors for diabetes mellitus appear after the age of 45 years. This is because people at this age are less active, gain weight, decrease muscle mass, and are aging, which results in the progressive shrinkage of cells. In addition, the incidence of diabetes increases with age, especially at the age of >40 years, because at that age, glucose intolerance begins to increase.[10]

According to data on the use of oral anti-diabetic drugs by patients, some were given as single therapy and some were combined to be more effective than monotherapy. From Table 1, it can be seen that the most common monotherapy is metformin (46%). Metformin is recommended as the first-line treatment for most people with T2DM, according to PERKENI (2019).[11]

Creatinine clearance is the plasma volume cleared of creatinine in a given time. This creatinine clearance is reported in ml/min and can be corrected for body surface area. It is a non-absolute measurement of GFR but can provide information about the estimated GFR value. The measurement of creatinine clearance with the calculation formula becomes the standard for determining GFR. The formula for calculating

ISSN:2087-0337
E-ISSN:2715-9949

creatinine clearance that can determine GFR is based on serum creatinine, sex, and body weight without requiring urine creatinine data and is called the Cockroft and Gault formula.[12] The creatinine clearance value of each patient was calculated using the Cockroft and Gault formula, then grouped by stage of kidney damage as can be seen in table 2.

The results of creatinine clearance in DM patients with impaired renal function at dr. Soekardjo Tasikmalaya Hospital based on the Cockroft and Gault formula showed that the majority of patients had creatinine clearance below 50 mL/minute. The decrease in creatinine clearance can be influenced by several factors, such as degenerative diseases, obesity, aging, and the use of drugs that can damage the kidneys. To prevent further kidney damage, avoid taking drugs with nephrotoxic potential or adjust the dosage of these drugs according to the ability of kidney function.[13]

After calculating the creatinine clearance (CrCl) from each patient, the suitability of the oral antidiabetic dose obtained by the patient was checked by comparing it with the literature dose, which can be seen in Table 3. This can be seen in the data in Table 4. The dose mismatch in these patients will certainly have a negative impact on the patient because it is feared that it can worsen the patient's condition. Because the purpose of giving a drug with a dose is to be able to produce a drug therapy effect with a certain intensity, the diagnosis and selection of the right drug are also important factors in therapy's success.[14]

Based on the results of the study in Table 5, it can be seen that the majority of type 2 DM patients with impaired kidney function (71.43%) received doses that were not in accordance with the literature, and where all were inappropriate, the doses obtained by patients were higher than they should be. As a result, 25 of the 35 patients mentioned above required a dose adjustment in their therapy. Based on Table 4, it is explained that treatment with alpha-glucosidase inhibitors (acarbose) is not recommended because it refers to the results of the patient's creatinine clearance and the comparative literature, so it would be better for the treatment of patients with acarbose to be reviewed to achieve the desired therapeutic effect and avoid more severe kidney damage. Other drugs such as glimepiride, glibenclamide, and metformin also require dose adjustments according to the patient's creatinine clearance value to avoid unwanted side effects.

Metformin is the most commonly used drug in dr. Soekardjo Tasikmalaya Hospital; of the 35 patients, 26 received metformin therapy, either monotherapy or in combination with other oral antibiotics, with 21 receiving inappropriate doses. Despite the fact that metformin is typically used as first-line therapy in diabetes therapeutic algorithms, it has several advantages, including a low risk of hypoglycemia. Metformin is absorbed slowly after oral administration, reaches its maximum concentration within 1 to 3 hours after ingestion, and is excreted immediately within 4–8 hours. In patients with moderate and severe renal function impairment, Cmax will increase by 173% and 390%, respectively, when compared to patients with normal kidneys. Metformin is actively excreted through the urinary tract in an unchanged form. It is also absorbed in the intestine and is mediated by transporters known as plasma membrane monoamines. The kidneys will actively secrete metformin after it has been processed in the renal tubules and will be excreted into the lumen. Thus, metformin increases the risk of lactic acidosis when renal function declines. If renal function is not monitored during the administration of metformin, it will

worsen kidney conditions and increase the risk of renal perfusion. Monitoring is carried out in the form of monitoring urine output and serum creatinine.[15]

After metformin, glimepiride is the drug that is widely used; from 35 samples, 17 of them were given glimepiride. Most of the doses given are not in accordance with the patient's kidney condition. In patients with impaired renal function stage 4-5, the use of glimepiride is quite dangerous and needs to be monitored further because glimepiride is metabolized by the liver into two main metabolites, both of which have hypoglycemic activity. Both of these metabolites will be accumulated in the kidneys, and in patients with renal impairment, they will cause severe hypoglycemic effects that can last for more than 24 hours.[15]

Subsequently, 7 of 35 patients were treated with acarbose, with all patients receiving inappropriate doses. The use of acarbose in DM patients with impaired renal function is very rare, so acarbose is contraindicated in patients with impaired renal function.[16] Therefore, in the absence of detailed research on the effects of using acarbose on patients with impaired renal function, it is very important to pay attention to the administration of doses that are tailored to the patient's kidney condition.[17]

One other patient was treated with glibenclamide, and the dose was not appropriate. Glibenclamide is metabolized in the liver and will be excreted by the kidneys and intestines. The active metabolites produced will be accumulated in the kidneys. In patients with impaired renal function, administration of glibenclamide that is not suitable for kidney conditions can cause serious hypoglycemic effects and last for more than 24 hours. The use of glibenclamide is contraindicated in patients with impaired renal function, stage 3, with CrCl 60 ml/min.[15]

Dosage discrepancies are one of the discrepancies in treatment. This is caused by many factors, which are divided into two groups, namely the causes at the patient level and the system level. Causes at the patient level include patient non-compliance when taking medication, unwanted drug reactions, no time for patients to redeem prescriptions, and self-medication. Meanwhile, at the system level, there is conflicting information from various available information sources, instructions to patients when services are insufficient, and issues with drug availability or drug dosages, among other things.[18]

As the side effects of each drug have been described, the mismatch of drug doses given to type 2 DM patients with impaired renal function greatly affects the patient's condition. The most common effect found is serious hypoglycemia that lasts for more than 24 hours. This can occur due to a lack of monitoring of the patient's condition, the availability of drugs, side effects after therapy, a lack of attention to patients, and a lack of awareness in dose adjustment therapy. As a result, the patient's condition may worsen, the desired therapeutic effect may not be achieved, and, in the worst-case scenario, chronic kidney failure may result.

Conclusion

Based on the results of research that has been carried out regarding the suitability of drug doses for type II diabetes mellitus patients with impaired kidney function at dr. Soekardjo Tasikmalaya Hospital, it can be concluded that from 35 samples, as many as 25 people, or 57.15% of patients, received therapeutic doses that did not follow their kidney conditions. Meanwhile, 10 people, or 42.85% of patients, received a therapeutic dose according to their kidney condition.

ISSN:2087-0337
E-ISSN:2715-9949

Acknowledgement

The author would like to thank the Faculty of Mathematics and Natural Sciences UNIGA which has assisted in funding this research.

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