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DRUG PATTERN STUDY ON ANGIOTENSIN II RECEPTOR BLOCKER IN OUTPATIENTS AT MOHAMMAD HOESIN HOSPITAL PALEMBANG

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ABSTRACT

Hypertension is a global health problem due to its increasing prevalence. Hypertension is a condition where there is a persistent increase in blood pressure exceeding 140/90 mmHg. Among the many choices of antihypertensive drug classes, ARB is one of the first-line drug classes for the treatment of hypertension. Inappropriate ARB administration can reduce the effectiveness of treatment and harm the patient. This study aims to determine the pattern of ARB use in hypertensive patients. This drug pattern study has been done on October – November 2021 at the Outpatient Department of Dr. Mohammad Hoesin Central Public Hospital Palembang. The sample was using the medical record data of all hypertensive patients' period of July – December 2020 who met the inclusion criteria, with a total of 171 data. The data was processed by using the SPSS v25 and presented in the form of a table with a descriptive explanation referring to the research variables. This study found that the prevalence of ARB use was 59.0% with the highest was in male (30.4%) and age group 41-60 years (29.2%). The most widely used ARB is candesartan (94.0%) at a dose of 16 mg (52.6%), frequency once a day (97.9%) and duration more than one month (93.7%). The drug prescribed to the patient mostly didn't have interaction with ARB (33.0%). The prevalence of ARB administration is high in hypertensive patients (59.0%) with the most commonly used ARB is candesartan (94.0%).

Keywords: hypertension, ARB, drug pattern study

1. INTRODUCTION

Based on JNC VII, the diagnosis of hypertension can be established if the systolic blood pressure is ≥ 140 mmHg and the diastolic blood pressure is ≥ 90 mmHg.[1] The prevalence of hypertension is increasing globally due to aging of the population and increased exposure to lifestyle risk factors, including unhealthy diet and physical inactivity.[2] According to the National report, Riskesdas 2018, based on measurements in people aged ≥ 18 years, the prevalence of hypertension in Indonesia reached 34.1%.[3] Uncontrolled hypertension can cause damage to a number of important organs (target organ damage), such as the heart, kidneys, brain, and retina, even hypertension can cause erectile dysfunction.[4] As a high risk factor for various diseases, hypertension needs to be detected early by routinely checking blood pressure and hypertension must be controlled in order to reduce morbidity and mortality rates.

Management of hypertension consists of non-pharmacological therapy (lifestyle modification) and pharmacological therapy. Non-pharmacological therapy should be carried out by all patients with hypertension to prevent the development of hypertension, gradually control blood pressure, and can increase the effect of treatment in patients with a significant increase in blood pressure. The importance of lifestyle changes such as maintaining an ideal body weight, reducing salt consumption, regular aerobic exercise, quitting smoking and

limiting alcohol consumption can reduce blood pressure, increase the effects of antihypertensive drug therapy, and prevent the risk of cardiovascular disease.[1,5,6] In controlling hypertension, apart from changing lifestyle, the choice of antihypertensive drugs is also very diverse. There are several published guidelines on the classification of hypertension to assist physicians in achieving proper hypertension control.[7]

On the other hand, the decision to initiate pharmacologic therapy is based on the stage and severity of hypertension, presence of target organ disease, and the presence of other disease conditions and risk factors.[1] The goal of drug therapy is to use the selected therapeutic agent, either singly or in combination, to restore blood pressure to normal levels with minimal side effects, so the selection of antihypertensive drugs also needs to consider efficacy, safety, impact on quality of life, compliance, ease of administration, and cost.[8] Each individual will have different indications for choosing a particular antihypertensive as a first-line drug, the choice of drug for hypertension is influenced by age, comorbidities, ethnicity, pregnancy, and other parameters.[5,9]

Different classes of antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARBs), beta-blockers (BB), calcium channel blockers (CCBs), and diuretics are available as monotherapy or as combination therapy for effective management from hypertension. The selection of the right antihypertensive drug must be based on positive indications, contraindications, the presence or absence of comorbidities, and conditions that require careful drug use.[10] Among the many choices of antihypertensive drug classes, ARBs are one of the groups that are widely used as therapy options in the community. This is because ARBs are one of the first-line drug classes for the treatment of hypertension. Good effectiveness and minimal side effects are one of the reasons for the high number of ARB prescriptions in hypertensive patients.[11,12]

Angiotensin receptor blockers (ARBs) are active compounds that are competitive antagonists of the angiotensin II type 1 receptor. Administration of AT1 receptor antagonists results in a decrease in total peripheral resistance (afterload) and cardiac venous return (preload). All physiological effects of angiotensin II, including stimulation of aldosterone release, are inhibited in the presence of AT1 receptor antagonists. ARBs have the advantage of more complete blockade of the action of angiotensin II, because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II. Furthermore, ARBs do not affect bradykinin levels and are therefore associated with a lower incidence of cough. While all AT1 receptor antagonists are effective in the treatment of hypertension, several comparative studies have suggested that longer-acting AT1 receptor antagonists, such as irbesartan, candesartan, and telmisartan, may be more effective in controlling 24-hour blood pressure. ARBs slow the progression of diabetic nephropathy and valsartan has been reported to reduce the incidence of diabetes in patients with impaired glucose tolerance. It is also effective in the treatment of heart failure and as an alternative when ACE inhibitors are not well tolerated.[13–15]

One of the most essential problems facing public health care providers and administrators in many countries is the irrational use of drugs, and therefore the concept of rational use of drugs over the past few years has been the theme of various national and international meetings. Various studies conducted in developing and developed countries over the last few years regarding the safe and effective use of drugs show that irrational drug use is a global phenomenon, and few prescriptions demonstrate rational drug use. The irrational use of drugs has many consequences including treatment ineffectiveness, unnecessary drug prescribing, development of resistance, side effects, and economic burden on patients and society. Therefore, the prescriber must make an accurate diagnosis and prescribe rationally.

The study of drug prescribing patterns is an important part of a medical audit that seeks to monitor drug use patterns and the necessary modifications to these patterns to achieve rationality and cost-effective drug use.[16] The study of antihypertensive drug use pattern is one of the most widely carried out due to the high prevalence of hypertension so that the use of antihypertensive drugs also continues to increase. In Indonesia, antihypertensive drug use pattern study have also been carried out as part of the evaluation of therapy so that patients always receive rational treatment. The results of these studies are very diverse. However, there has been no specific research on the pattern of antihypertensive use in Palembang or specific research on the pattern of using antihypertensive ARBs, therefore this study can be a new reference for antihypertensives in the ARB class in Palembang and become a reference for future research.

2. METHOD

This research using medical records data of hypertensive patients who seek treatment at the Outpatient Department of Mohammad Hoesin Central Public Hospital Palembang in July – December 2020. Inclusion criteria included patients with hypertension who had a complete medical record history, data in the medical record had data on administration of antihypertensive drugs and medical records for patients aged 18 years. The sampling method is by total sampling, which is as many as 171 samples. Subsequently, data was recorded on the results of patient identification medical records, medical history, and data on ARB drug administration (type of drug, frequency of administration, duration of administration, and drug interactions). All research data obtained will be analyzed with SPSS v25 and presented in tabular form accompanied by a descriptive explanation. The success parameter of this research is to know the pattern of using antihypertensive group ARB in hypertensive patients in Dr. RSUP. Mohammad Hoesin Palembang period July – December 2020.

3. RESULTS

The analysis results of the prevalence of ARB use from 171 samples 101 (59%) using ARB. The proportion of ARB use by age and gender can be seen in the table below.

Table 1. Prevalence of ARB Use by Age and Gender

Age group	ARB				Total	
	Yes (n=101)		No (n=70)			
	n	%	n	%	n	%
18 – 40	14	8.2	10	5.8	24	14.0
41 – 60	50	29.2	37	21.7	87	50.9
> 60	37	21.6	23	13.5	60	35.1
Gender						
Male	52	30.4	40	23.4	92	53.8
Female	49	28.6	30	17.6	70	46.2
Total	101	59.0	70	41.0	171	100

The proportion of ARB use by type can be seen in the table 2.

Table 2. Proportion of use of ARB type

ARB type	Total	Percentage (%)
Candesartan	95	94.0
Valsartan	3	3.0
Telmisartan	2	2.0
Irbesartan	1	1.0
Total	101	100.0

The proportion of candesartan administration can be seen in the table 3.

Table 3. Proportion of candesartan administration

ARB administration		Total	Percentage (%)
Dose	16 mg/day	50	52.6
	8 mg/day	45	47.4
Frequency	Once a day	93	97.9
	Twice a day	2	2.1
Duration	> 1 month	89	93.7
	≤ 1 month	6	6.3
Total		95	100.0

The proportion of other ARBs administration can be seen in the table 4.

Table 4. Proportion of other ARBs administration

ARB type	Dose	Frequency once a day	
		> 1 month	
		n	%
Valsartan	160 mg/day	1	16.7
	80 mg/day	2	33.2
Telmisartan	40 mg/day	1	16.7
	80 mg/day	1	16.7
Irbesartan	300 mg/day	1	16.7
Total		6	100.0

Drug interaction can be seen in the table 5.

Table 5. Drug Interaction

Interaction	Total	Percentage (%)
Synergistic	129	30.0
Antagonist	42	9.8
Potentiation	117	27.2
No interaction	142	33.0
Total	430	100.0

4. DISCUSSION

ARB is one of the first-line antihypertensive therapy drugs recommended by all international guidelines, this is due to its high effectiveness and minimal side effects so it can be well tolerated as a monotherapy regimen, or used in combination therapy with other antihypertensive drugs and is used as a mainstay in the treatment of stage I and II hypertension.[17] In a study by Kim, et al in 2019 it was found that ARBs were the most widely prescribed antihypertensive group in Korea, which was 51.6% of the total 2,919,162 research subjects. It is said that ARBs are also the most widely prescribed antihypertensives in Japan and China. This is thought to be due to the advantage of fewer side effects from ARBs. In addition, the decrease in the prescription of ACE inhibitors is also thought to cause an increase in ARB which is an alternative to ACE inhibitors.[18]

Based on this study, it was found that the most users of ARB as an antihypertensive therapy regimen were patients in the 41-60 years age group (29.2%) and male patients (50.4%). This finding is in accordance with National Institute for Health and Care Excellence (NICE) guideline in 2011 where ARBs and ACE inhibitors are recommended for patients age under 55 year.[10,11] A study in 2015 by Xie et al. in China also found that male patients have higher rates of ACEI/ARB use in patients with type 2 diabetes and hypertension.[19]

The increasing prevalence of candesartan use is thought to be due to switching from other types of ARB drugs used by patients, it was said that the withdrawal of generic drug products containing ARBs due to possible contamination of carcinogenic nitrosamines led to a fast and substantial decrease in valsartan. To compensate, there was an increase in the use of candesartan, resulting in an increase in total ARB prescriptions. Therefore, the data suggest that patients initially receiving treatment with an ARB, continue to be switched primarily to other types of ARB, mostly from valsartan to candesartan.[20] In addition, data in the UK show that candesartan is the most widely used ARB, accounting for almost a third of all ARBs prescription, presumably because it is cheaper than other ARBs.[21]

This study found that all patients received candesartan at the right dose and frequency of administration. In the management of hypertension, the usual starting dose of candesartan is 16 mg once daily, and based on the blood pressure response or side effects of candesartan, the dose may be increased or decreased, the dose may be increased to 32 mg daily, as a single dose or in two divided doses. The usual maintenance dose is 8 mg once daily. Candesartan can be given once or twice daily for a total daily dose ranging from 4 mg to 32 mg. If the dose given is less than the recommended dose range then therapy will not be able to achieve maximum results, in this case the patient will not reach a state of normotension, on the contrary if the dose given exceeds the maximum recommended it can cause side effects of the drug.[22,23] The frequency of giving candesartan once a day is probably due to the consideration that

candesartan is a long-acting and effective drug even though it is only given once a day. With once-daily dosing, the blood pressure-lowering effect is maintained for 24 hours with a peak ratio generally over 80%.[24] However, from the results of this study, it was also found that there was still the use of candesartan for ≤ 1 month. This indicates that there are still 6.3% of candesartan prescriptions that are not in accordance with the candesartan administration recommendation. The antihypertensive effect of candesartan can indeed be seen within 2 weeks, but the maximum effect can only be achieved after giving therapy for about 4 to 6 weeks from the time of starting therapy, so taking candesartan for less than 4 weeks can be said to be inappropriate.[22,25]

The results of this study found that the proportion of valsartan doses prescribed was 160 mg/day in 1 patient and 80 mg/day in 2 patients, this is in accordance with the recommended dose variation in therapy using valsartan, where in hypertension therapy, valsartan is given in an initial dose of 80 mg once daily and may be increased to 160 mg once daily. Valsartan can be used in a dose range of 80 mg to a maximum of 320 mg daily.[26,27] While the use of telmisartan, 1 patient received a dose of 40 mg/day and another patient received a dose of 80 mg/day, this is also in accordance with the therapeutic guidelines from telmisartan, where the dose range of telmisartan is 20 mg to a maximum of 80 mg daily, with the initial therapeutic dose used usually being 40 mg once a day.[25,28] In addition, patients receiving therapy with irbesartan are given a dose of 300 mg/day, this dose is also appropriate according to the dose range of irbesartan, which is 75 mg to a maximum of 300 mg a day, meanwhile the initial dose of irbesartan which is usually used is 150 mg once a day.[29,30]

In the use of ARBs other than candesartan, there was no frequency of drug administration more than once a day or duration of drug administration less than 1 month. This is in accordance with the guidelines for prescribing the three drugs, where the recommended consumption of valsartan, telmisartan and irbesartan is 1 time a day.[26,28,29] In addition, the duration of administration of the three drugs is also appropriate because the antihypertensive effect of valsartan and telmisartan will be seen within 2 weeks after starting therapy and the maximum effect can be seen in 4 weeks, while for valsartan the antihypertensive effect will be seen in 4 to 4 weeks. 6 weeks after starting therapy.21eeks after starting therapy and the maximum effect can be seen within 4 weeks, while for valsartan the antihypertensive effect will be seen within 4 to 6 weeks after starting therapy.[25]

A drug interaction is a modification of the effect of a drug due to another drug given initially or given concurrently, so that the effectiveness or toxicity of one or more drugs changes. Drug interactions are divided into 3 types, namely synergistic, antagonistic and potentiation interactions. Mechanisms of drug interactions can occur due to interactions involving the pharmacokinetic aspects of drugs or interactions that affect the pharmacodynamic response of drugs.[31] Drug interactions can be classified as desired and unwanted interactions. Synergistic interactions that result in increased therapeutic effects are expected drug interactions. However, antagonist and potentiation interactions often cause adverse drug reactions, namely when the metabolism of a drug is disturbed due to the presence of other drugs, causing an increase in plasma drug levels and toxicity. In addition, unexpected interactions between drugs can reduce treatment efficacy, develop resistance, decrease patient compliance in continuing treatment, and increase therapy costs due to additional doses and regimens that must be given to patients.[32]

For ARBs too there are several medications that can't be given together because it may cause drug interactions. Hyperkalemia can occur if ARBs are given with potassium supplements, potassium-sparing diuretics, or other drugs that can cause hyperkalemia. Concurrent use of aliskiren and ARBs may also increase the risk of hyperkalemia. ARBs and potassium-sparing diuretics (such as amiloride

and the aldosterone antagonists, eplerenone and spironolactone) generally should not be co-administered. Symptomatic hypotension may occur when therapy with ARBs is initiated in patients taking high-dose diuretics. The combination of NSAIDs and candesartan can cause blood pressure to rise or may cause swelling (edema), especially in patients with congestive heart failure (CHF), and may increase the risk of renal impairment and hyperkalemia, especially in patients who are not adequately hydrated. Increased serum lithium concentrations and lithium toxicity may occur when lithium and ARBs are given together. Since candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effect on P450 enzymes, interactions with drugs that inhibit or are metabolized by these enzymes will not occur.[25,33] Therefore, doctors must consider or make adjustments if they have to prescribe ARBs with these drugs.

5. CONCLUSION

Although there are many antihypertensive drugs, ARB is one of the most commonly use antihypertensive therapy regimens in Mohammad Hoesin Central Public Hospital Palembang because of its effectiveness (59.0%) and candesartan is the most frequently chosen ARB (94.0%).

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