POTENTIAL DRUG-DRUG INTERACTION IN ELDERLY PATIENTS IN TREATMENT WITH ANTIHYPERTENSIVE

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Abstract: Antihypertensive medications are often used in combination. This can increase the potential for drug interactions, which may lead to adverse drug reactions and affect the efficacy and safety of each drug. Elderly patients are at a higher risk of drug-related problems due to declining organ function, increasing the risk of complications from other diseases. Method: This study used a cross-sectional design with an observational approach. The data used was prescriptions from Karya Sehat Pharmacy from January to March 2024. Potential interactions were identified using UpToDate's Lexidrug database. Results: There were 122 prescriptions (29.53%) with the potential for drug interactions, with a total of 184 potential interactions consisting of 7 potential (3.80%) minor interactions, 172 potential (93.48%) moderate interactions, and 5 potential (2.72%) major interactions. Based on the mechanism, 85 potentials (46.20%) were pharmacokinetic, 90 potentials (48.91%) were pharmacodynamic, and 9 potentials (4.89%) were unknown. Conclusion: There is a potential for drug interactions in antihypertensive prescriptions for elderly patients, which can affect the efficacy and safety of the medication. Most drug interactions occurred at the pharmacodynamic phase and a moderate severity level. Management of interactions begins with patient education, monitoring the patient's clinical condition, therapy modification, or recommending therapy replacement.

Keywords: potential drug interactions, antihypertensive, elderly

A. Introduction

One of the leading causes of death worldwide is cardiovascular disease, including hypertension. Hypertension is defined as elevated blood pressure, with a systolic blood pressure (SBP) of 140 mmHg and a diastolic blood pressure (DBP) of 90 mmHg.[1] A total of 1.4 billion adults suffer from hypertension, and less than 14% of them have their blood pressure controlled with antihypertensive medication.[2] The prevalence of hypertension in Indonesia, according to the Badan Litbangkes in 2018, is 34.11%, and based on data from the Dinas Kesehatan Provinsi Jawa Tengah in 2021, the prevalence of hypertension in Central Java Province is 37.57%.[4] According to the Ministry of Health (2019),4 hypertension is most prevalent in 55-64 years (55.2%).

Initial management of hypertension therapy is typically administered as monotherapy. However, if monotherapy proves ineffective, combination therapy can be introduced. Combination therapy for hypertension may involve pairing antihypertensive drugs with other medications, especially if the patient has comorbid conditions.[5] The duration of antihypertensive use is usually long-term, necessitating close attention to prevent drug

interactions and ensure therapeutic effectiveness.[6] Using two or more medications can increase the likelihood of adverse outcomes, one of which is the heightened risk of drug interactions. Drug interactions are a significant factor in drug-related problems that can affect patient therapy outcomes.[7]

Drug interactions can affect the treatment provided, resulting in either desired reactions, such as increased drug effectiveness, or undesired reactions, such as therapeutic failure.[8,9] This makes elderly patients more susceptible to drug interactions due to decreased organ function and the likelihood of polypharmacy, which increases the risk of other complications from hypertension, such as diabetes mellitus, stroke, and dyslipidemia.[4] This study aims to obtain an overview of the potential drug interactions involving antihypertensive medications in elderly patients receiving antihypertensive treatment.

B. Methods

This is a descriptive observational study. Data collection is conducted prospectively on antihypertensive prescriptions for elderly patients from January to March 2024, with each prescription containing at least two types of medications, one of which is an antihypertensive. Sampling is performed using the random sampling method. The research instruments include antihypertensive prescriptions, a database, and scientific literature to identify potential drug interactions. The evaluation of possible drug interactions is theoretically based on literature studies. The data from each prescription will be reviewed for interaction potential using the Drug Interaction Checker from UpToDate. The percentage of antihypertensive drug interactions will be determined, including the interaction mechanisms based on severity and interaction mechanism, as well as identifying the types of drugs that frequently interact.

C. Results And Discussion

1. Description

A total of 413 prescriptions met the inclusion criteria. Table I presents the gender distribution of the patients. The table shows that the number of prescriptions for female patients is higher, with 302 prescriptions (73.12%) compared to 111 prescriptions for male patients (26.88%).

Table II shows that 10 types of antihypertensives are prescribed. The most frequently prescribed antihypertensives are amlodipine (n = 425, 42.00%), bisoprolol (n = 185, 18.28%), valsartan (n = 163, 16.10%), and candesartan (n = 113, 11.17%).

Table III shows the number of potential drug interactions. There are 122 prescriptions (29.54%) that have potential drug interactions, with a total of 184 potential interactions identified. In this study, the potential interactions were analyzed based on their mechanism and severity. The interaction mechanisms are categorized into two types: pharmacokinetic and pharmacodynamic. The severity levels are divided into minor, moderate, and major. The distribution of potential interactions by severity is shown in Table IV, which indicates that 3.26% are minor, 93.48% are moderate, and 3.26% are major. Table V presents the potential interactions based on mechanism, with 46.20% being pharmacokinetic and 48.91% pharmacodynamic.

2. Figures and Tables

Table 1. Patient demographics

Gender	Frequency (n=413)	Percentage (%)
Male	111	26.88
Female	302	73.12

Tabel 2. Number of antihypertensive drug use

Drugs	Frequency (n=1.012)	Percentage (%)
Amlodipine	425	42,00
Bisoprolol	185	18,28
Valsartan	163	16,10
Candesartan	113	11,17
Furosemide	67	6,62
Spironolakton	22	2,17
Lisinopril	15	1,48
Captopril	10	0,99
Irbesartan	8	0,79
Ramipril	4	0,40

Table 3. Potential drug interactions

Potential drug interactions	Frequency (n=413)	Percentage (%)
Ada interaksi obat	122	29.54
Tidak ada interaksi obat	291	70.46

Table 4. Frequency severity of drug interactions

Severity	Frequency (n=184)	Percentage (%)
Minor		
Lisinopril - acarbose	1	0.54
Lisinopril - glimepiride	1	0.54
Hidroklortiazid - valsartan	3	1.63
Captopril - glimepiride	1	0.54
Total	**6**	**3.26**
Moderat		
Amlodipine - simvastatin	76	41.30
Bisoprolol - metformin	17	9.24
Amlodipine - furosemide	13	7.07
Bisoprolol - glimepiride	12	6.52
Candesartan - furosemide	6	3.26
Furosemide - glimepiride	5	2.72
Bisoprolol - furosemide	4	2.17
Bisoprolol - acarbose	4	2.17
Furosemid - acarbose	4	2.17
Furosemid - metformin	4	2.17
Furosemid - valsartan	4	2.17
Bisoprolol - nitrokaf	2	1.09
Furosemid - spironolakton	2	1.09
Hidroklortiazid - glimepiride	2	1.09
Amlodipine - furosemide	1	0.54
Bisoprolol - ISDN	1	0.54
Candesartan - nitrokaf	1	0.54
Captopril - furosemide	1	0.54
Captopril - metformin	1	0.54
Furosemide - aspirin	1	0.54
Furosemide - nitrokaf	1	0.54
Furosemide - digoxin	1	0.54
Lisinopril - nitrokaf	1	0.54
Lisinopril - metformin	1	0.54
Lisinopril - furosemide	1	0.54
Hidroklortiazid - nitrokaf	1	0.54
Hidroklortiazid - glimepiride	1	0.54
Hidroklortiazid - acarbose	1	0.54
Nifedipin - bisoprolol	1	0.54
Nifedipine - nitrokaf	1	0.54
Valsartan - ISDN	1	0.54
Total	**172**	**93.48**
Mayor		
Candesartan - spironolakton	4	2.17
Ramipril - spironolakton	1	0.54
Captopril - spironolakton	1	0.54
Total	**6**	**3.26**

Tabel 5. Frequency of drug interaction mechanisms

Mechanism	Frequency (n=184)	Percentage (%)
Pharmacokinetics		
Amlodipine - simvastatin	76	41.30
Furosemide - metformin	4	2.17
Hidroklortiazid - valsartan	3	1.63
Captopril - spironolakton	1	0.54
Furosemide - digoxin	1	0.54
Total	**85**	**46.20**
Pharmacodynamic		
Bisoprolol & Metformin	17	9.24
Amlodipine & Furosemide	13	7.07
Bisoprolol & Glimepiride	12	6.52
Candesartan & Furosemide	6	3.26
Furosemide & Glimepiride	5	2.72
Bisoprolol & Glimepiride	4	2.17
Bisoprolol & Acarbose	4	2.17
Candesartan & Spironolakton	4	2.17
Furosemide & Acarbose	4	2.17
Furosemide & Valsartan	4	2.17
Bisoprolol & Nitrogliserin	2	1.09
Furosemide & Spironolakton	2	1.09
Amlodipin & Nitrogliserin	1	0.54
Bisoprolol & ISDN	1	0.54
Candesartan & Nitrogliserin	1	0.54
Captopril & Furosemide	1	0.54
Furosemide & Aspirin	1	0.54
Furosemide & Nitrogliserin	1	0.54
Lisinopril & Nitrogliserin	1	0.54
Lisinopril & Furosemide	1	0.54
Hidroklorotiazid & Nitrogliserin	1	0.54
Nifedipin & Bisoprolol	1	0.54
Nifedipin & Nitrogliserin	1	0.54
Ramipril & Spironolakton	1	0.54
Valsartan & ISDN	1	0.54
Total	**90**	**48.91**
Unknown		
Hidroklorotiazid & Glimepiride	2	1.09
Captopril & Glimepiride	1	0.54
Captopril & Metformin	1	0.54
Lisinopril & Acarbose	1	0.54
Lisinopril & Glimepiride	1	0.54
Lisinopril & Metformin	1	0.54
Hidroklorotiazid & Metformin	1	0.54
Hidroklorotiazid & Acarbose	1	0.54
Total	**9**	**4.89**

Most patients were female, with 302 patients (73.12%) compared to 111 male patients (26.88%). A study by Wahyuni (2013)[10] also reported that women are more likely to suffer from hypertension than men. This is because women experience menopause, during which their estrogen levels decrease. Low estrogen levels cause blood to become thicker, increasing the risk of blood clotting. In postmenopausal women, low estrogen levels are typically

accompanied by a decrease in HDL levels if not coupled with a healthy lifestyle. This can lead to atherosclerosis, resulting in elevated blood pressure.[11]

The total number of antihypertensive medications in the sample was 1,012. Amlodipine dominated usage with 425 instances (42%), followed by bisoprolol with 185 cases (18.28%), and valsartan with 163 cases (16.10%). Amlodipine is a Calcium Channel Blocker (CCB) and is frequently used due to its strong blood pressure-lowering effect compared to other types.[12] Additionally, amlodipine is considered a first-line therapy for hypertension according to the JNC 8 guidelines. Amlodipine shares a mechanism similar to other dihydropyridine calcium antagonists by relaxing the arterioles. It is vascular-selective, has relatively low oral bioavailability, a long half-life, and slow absorption, which helps prevent a sudden drop in blood pressure.[13]

There were 122 prescriptions (29.54%) with drug interactions and 291 prescriptions (70.46%) without drug interactions. Of the 122 prescriptions with drug interactions, 95 prescriptions (77.87%) had one potential drug interaction, 11 prescriptions (9.01%) had two potential drug interactions, and 16 prescriptions (13.12%) had 3-5 potential drug interactions. The occurrence of drug interactions is likely due to the decreased organ function in geriatric patients, necessitating close monitoring of drug interactions. This view is supported by research from James et al. (2014)14, which states that as age increases, the likelihood of comorbid conditions also rises due to declining organ function.

The severity of drug interactions is classified into three levels: minor, moderate, and major. The most frequent interaction identified was between amlodipine and simvastatin, occurring 76 times (41.30%). This interaction is categorized as moderate in severity with a pharmacokinetic excretion mechanism. This drug combination is often prescribed together because of its effectiveness in stabilizing blood pressure and lowering cholesterol levels in patients.[15] However, this combination can increase the concentration of simvastatin. The mechanism involves amlodipine inhibiting the CYP3A4 enzyme, which is responsible for the metabolism of simvastatin, leading to an increased concentration of simvastatin and a higher risk of simvastatin toxicity, such as myopathy and rhabdomyolysis. This can be managed by adjusting the daily dose of simvastatin, which should not exceed 20 mg in patients taking amlodipine. Another option is to switch to other statins not metabolized by the CYP3A4 enzyme, such as fluvastatin, pravastatin, or rosuvastatin.[16,17]

Based on their mechanisms, drug interactions are divided into two categories: pharmacokinetic and pharmacodynamic interactions. The most common pharmacokinetic interactions were amlodipine and simvastatin, which interact through pharmacokinetic metabolism. In the pharmacodynamic phase, synergistic interactions were observed, such as between amlodipine-furosemide, lisinopril-furosemide, and spironolactone-furosemide, where each drug enhances the hypotensive effects of the others. Furosemide lowers blood pressure by reducing the volume of fluid in the blood vessels (plasma volume), leading to a decrease in blood pressure because the volume of blood flowing through the vessels is reduced, resulting in hypotension.[5] When furosemide is combined with other blood pressure-lowering drugs, the risk of hypotension increases. However, the combination of furosemide with antihypertensives can still be used with careful monitoring for signs and symptoms of hypotension and considering dosage adjustments for antihypertensive medications.[16]

Pharmacodynamic antagonistic drug interactions were also found between furosemide-acarbose and furosemide-glimepiride. Furosemide can cause hyperglycemia in patients with diabetes mellitus, which is contrary to the goal of antidiabetic therapy, which is to lower blood sugar levels. The mechanism of this hyperglycemia has not been fully explained. However, the most commonly mentioned hypothesis is the hypokalemia effect caused by using furosemide. Several studies have reported that low potassium levels are associated with increased blood

sugar levels. This interaction can be managed by reducing the dose of furosemide or increasing the dose of antidiabetic drugs and regularly monitoring blood glucose levels.[16,18]

This research demonstrates that drug interactions among antihypertensive medications have significant implications for the efficacy and safety of hypertension treatment. The data obtained revealed that certain drug combinations can increase the risk of adverse effects, both those that are undesirable and those that enhance therapeutic efficacy. Therefore, medical practitioners must consider the potential for drug interactions when prescribing antihypertensive therapy to patients. A better understanding of these interactions can help optimize treatment, reduce the risk of adverse effects, and improve patients' quality of life. Further research is needed to explore these drug interactions' mechanisms further and develop more comprehensive clinical guidelines for hypertension management.

D. Conclusion

Out of the 413 samples obtained, 122 prescriptions (29.54%) had the potential for drug interactions at Karya Sehat Pharmacy from January to March 2024, totalling 184 potential drug interactions. These 184 potential drug interactions can be categorized into three mechanisms: pharmacokinetic (46.20%), pharmacodynamic (48.91%), and unknown mechanism (4.89%). Most drug interactions occurred at a moderate level (93.48%), followed by minor (3.26%) and major (3.26%). Management of pharmacokinetic interactions can involve dose adjustments and therapy replacement, while pharmacodynamic interactions can be managed by monitoring signs and symptoms of adverse drug reactions.

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