

POTENTIAL INTERACTIONS ANALYSIS OF ANTIHYPERTENSIVE DRUGS USED IN GERIATRIC

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ABSTRACT

Objective: Hypertension is a degenerative disease that increases with age. Elderly patients are at the highest risk due to organ function decreasing. Therefore, drug interactions are possible. This study determined the potential drug interactions, which aimed to assess the potential for drug interactions based on the mechanism and severity, and next, to determine the relationship between polypharmacy and drug interactions.

Methods: This research was conducted retrospectively using data from medical records of geriatric patients with hypertension at the outpatient polyclinic of RSI Ibnu Sina Padang for 2021. Purposive sampling was used in this study.

Results: A sample of 155 patients was included in the inclusion criteria. The data were checked using Stockleys Drug Interaction, Adverse Drug Interaction, and software on the Drug Interaction Checker (www.drugs.com), then analyzed descriptively using SPSS. The results showed that the number of potential drug-drug interactions was quite high at 63.2%. The most common mechanism pattern is pharmacodynamics (66.67%), with the highest severity of drug interactions being moderate (88%). The study showed a significant association between polypharmacy and drug interactions ($p=0.000$).

Conclusion: The active role of pharmacists is expected in monitoring drug use that can potentially cause drug interactions. This action can prevent unwanted events associated with concurrent drug use.

Keywords: Drug interactions, Geriatrics, Hypertension, Polypharmacy

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INTRODUCTION

Hypertension is a problem and a threat to the world. Hypertension has been recognized as the biggest disease contributor and cause of death in cardiovascular disease. Globally, one-third of the deaths are caused by cardiovascular disease, about 17 million people. Every year, 9.4 million of the total are caused by complications of hypertension [1]. Hypertension is also known as high blood pressure, where the occurrence of a condition of blood vessels increases the pressure continuously. Hypertension is when the systolic blood pressure is more than 140 mmHg and the diastolic blood pressure is more than 90 mmHg [1].

Hypertension is the highest prevalence of comorbidities in elderly patients with other chronic diseases [2]. The proportion of receiving antihypertensive drugs increases with age. Thus, hypertensive patients aged 80 y are often prescribed two or more antihypertensive drugs (about 1.25 million people in the UK) [3]. Along with the severity and duration of the disease, hypertension is usually accompanied by complications of other conditions, so the incidence of polypharmacy is very potential in prescribing hypertension. Based on the report of Riskesdas in 2018, the occurrence of hypertension based on the age measurement of the population is the highest experienced at the age of 75 y and over [4]. Thus, elderly patients should be a priority for doctors in providing appropriate treatment [5].

Polypharmacy comes from the Greek words: *poly*, meaning many, and *pharmakeia*, meaning drugs. So the term polypharmacy is used when a patient is taking multiple medications and when a doctor prescribes two or more drugs [6]. So polypharmacy is the use of drugs in large quantities that are not in accordance with the patient's health condition [7, 8].

Polypharmacy is often associated with adverse events such as adverse drug reactions (ADR), risk of falls, death, and length of hospital stay. Increasing the number of drug use in patients can increase the risk of side effects and drug hazards. The danger is caused by various factors, including drug and drug interactions [9, 10]. Polypharmacy can pose a high risk of drug interactions. Drug interactions can occur in two or more interacting drugs, which are

given initially or simultaneously so that they can affect the effectiveness of a drug and even cause toxicity. These drug interactions can be reduced by avoiding unnecessary polypharmacy treatments. So with the increasing use of medicines and polypharmacy practices, the potential for drug interactions will be even greater [6, 9]. In this case, the pharmacist is responsible for monitoring drug interactions and providing information about problems arising from drug interactions to doctors and patients [11].

Based on the illustration described above, this study aimed to analyze the potential for drug interactions in hypertensive patients at an outpatient polyclinic in a hospital in North Padang District.

MATERIALS AND METHODS

This research was conducted descriptively using retrospective data. Data obtained then were analyzed to see an overview of possible drug interactions based on the mechanism and severity of drug interactions using the Adverse Drug Interaction literature, Stockley's Drug Interaction, and the database on the Drug Interaction Checker (www.drugs.com) created by Wolters Kluwer Health, American Society of Health [7]. System Pharmacists, *Cerner Multum Inc.*® and *Micromedex*® from Truven Health [7]. The results of the data analysis showed potential drug interactions based on the mechanism and severity, as well as an analysis of the relationship between polypharmacy events and potential drug interactions using the Chi-Square and Fisher's exact test [12].

Population and sample

The quantity of samples in this research was calculated using the Slovin formula, based on the number of medical records of geriatric patients with hypertension during 2021 at the outpatient installation of RSI Ibnu Sina Padang, namely as follows [13]:

$$n = \frac{N}{1 + N(e^2)}$$

Where:

n = Number of samples

N = Total population

e = Margin of error

Number of samples needed in the study: $n = \frac{254}{1+254(0,05^2)}$

Based on the above formula, the sample required in this study amounted to 155. In addition, the data used in this study had several inclusion criteria: geriatric patients with hypertension at the Internal Medicine Polyclinic of RSI Ibnu Sina Padang from January to December 2021, patients diagnosed with hypertension with/without comorbidities, and geriatric patients aged above 60 y. Meanwhile, patients who did not have fixed registration numbers and medical records are excluded.

RESULTS AND DISCUSSION

Sociodemographic characteristics of the patient

In this study, a description of the sociodemographic characteristics of geriatric hypertension patients can be seen in table 1.

The majority of patients are women. This result is similar to a former study at 2021 that revealed more female than male patients experienced hypertension [14]. In the elderly, the risk of hypertension in women is higher than in men. This phenomenon is because women are protected by the hormone estrogen, which can increase High-Density Lipoprotein (HDL) levels before menopause. High levels of HDL can prevent atherosclerosis, which is considered the body's protective system. However, in women who enter the premenopausal period, the hormone estrogen will decrease little by

little so that there is a lack of protection against damaged blood vessels [15, 16].

The incidence of hypertension in geriatric patients is caused by arterial stiffness. Every year's increase in age will increase systolic blood pressure by 0.493 mmHg and diastolic blood pressure by 0.189 mmHg. This result is because the elasticity of blood vessels decreases with increasing age, increasing blood pressure [17]. Based on the existence and non-existence of comorbidities in geriatric patients with hypertension in this study, it was found that most patients had comorbidities, namely 85.8%. This number is in accordance with research conducted by Philia (2018) [18]. Elderly patients generally experience many comorbidities due to decreased body physiological functions. In addition, other factors, such as the pathophysiology of a disease that can cause different conditions, consumption of large amounts of drugs, and individual genetic factors, can affect the incidence of comorbidities in elderly patients [8, 19].

Drug prescribing patterns in geriatric hypertensive patients

Patients generally received less than five treatments (not polypharmacy) by 54.8%. This pattern shows that most of the patients at RSI Ibnu Sina who met the inclusion criteria did not receive more than five drugs. This grouping is intended because geriatric patients experience comorbidities, so polypharmacy events cannot be avoided [20].

Table 2 shows the types of drugs that are widely prescribed for geriatric hypertension patients

Table 1: Patients' characteristic

Patients' Characteristic	N	%
Age (year)		
60-74	109	70,3
75-90	44	28,4
>90	2	1,3
Gender		
Male	59	38,1
Female	96	61,9
Comorbidities		
With comorbidities	22	14,2
Without comorbidities	133	85,8

Table 2: Percentage of antihypertensive drugs use

No.	Drugs	Number of use	%
1	Amlodipine	106	40,0
2	Candesartan	86	32,5
3	Bisoprolol	24	9,1
4	Furosemide	14	5,3
5	Hydrochlorothiazide	10	3,8
6	Valsartan	8	3,0
7	Telmisartan	7	2,6
8	Spirolactone	3	1,1
9	Captopril	2	0,8
10	Lisinopril	2	0,8
11	Ramipril	2	0,8
12	Propranolol	1	0,4
Total		265	100,0

The percentage of antihypertensive drug use in table 3 above shows that the highest rate of drug use is amlodipine. This number is suitable with research by Fadhillah and Dharma (2020), in which amlodipine is the most widely used antihypertensive drug in hypertensive patients both as monotherapy and combination therapy and considering that amlodipine is a part of Calcium Channel Blocker (CCB) class drug which is a first-line antihypertensive, so amlodipine is often used in the treatment of hypertension [21].

Overview of potential drug interactions

The potential incidence of drug-drug interactions in hypertensive patients is quite high, at 63.2%. In prescribing hypertension, the types of drugs used are quite diverse and widely combined, so it is not easy to check potential interactions between drugs and drugs. Therefore, pharmacy installations in hospitals should be equipped with drug interaction checkers software to prevent interactions between drugs and drugs.

Table 3: Overview of potential drug interactions

Variable	Group	Interaction potential N= 98 (%)	Non-interaction potential N= 57 (%)
Age (year)	60-74	69 (70.4)	40 (70.2)
	75-90	27 (27.6)	17 (29.8)
	>90	2 (2.0)	0 (0.0)
Gender	Male	28 (28.6)	31 (54.4)
	Female	70 (71.4)	26 (45.6)
Comorbidities	With comorbidities	5 (5.1)	17 (29.8)
	Without comorbidities	93 (94.9)	40 (70.2)

Table 3 shows that patients aged 60-74 (elderly) has the highest potential for drug interactions in. The number of potential drug interactions in patients aged 60-74 y (elderly) can be influenced by various factors. For example, the number of treatments patients receive and the comorbidities experienced can lead to drug interactions. So it is very necessary to supervise health workers on the treatment received for patients of that age to prevent drug-related problems, one of which is drug-drug interactions. Distribution of patients by gender, most patients were female, as many as 70 people. However, some articles argue that gender is not related to the incidence of drug interactions, so gender is not a determining factor for drug interactions [22].

The distribution of patients with the potential to experience drug interactions based on comorbidities is generally experienced by patients with comorbidities [23]. Patients with comorbidities need many drugs to treat every disease condition, so the increasing number of prescription drugs can pose a potential risk of drug interactions [24].

Potential drug interactions based on the type of interaction

In this study, the most interactions were pharmacodynamic interactions of 66.67%. This result suggests that the drugs administered interact with each other, where the effect of one drug is altered by the other at the site of action. These interactions occur because drugs compete for certain receptors or the same physiological system [25].

Drug interactions with pharmacodynamic mechanisms that occur the most are amlodipine and bisoprolol interactions, diclofenac, and candesartan, with 14 cases each. Mechanism of interaction Amlodipine and bisoprolol have an additive effect in lowering blood pressure and heart rate, which can cause headaches, dizziness, fainting, and/or changes in pulse or heart rate [26]. Meanwhile, the mechanism of interaction between diclofenac and candesartan has an agonist effect so that the effect of candesartan in lowering blood pressure can be reduced by diclofenac [7].

The most common type of pharmacokinetic mechanism is the interaction of sucralfate and lansoprazole. These drug interactions occur at the absorption stage. For example, sucralfate can inhibit

absorption in the gastrointestinal tract, decreasing the effectiveness of lansoprazole [7].

Drug-drug interactions are of minor severity if they cause mild effects. These interactions may or may not interfere with the therapeutic effect significantly. Usually, no additional therapy is needed to treat it. In this study, the most frequent minor severity interactions were those between sucralfate and bisoprolol, ranitidine, and ketoprofen, with 3 cases each. The interaction mechanism between sucralfate and bisoprolol is not known with certainty but may involve the binding of cation beta-blockers or decreased dissolution rate due to increased gastric pH. So to prevent an increase in gastric pH during drug administration, consider separating the administration time of beta-blockers and sucralfate by at least 2 h [7]. The interaction between ranitidine and ketoprofen can cause changes in serum levels of ketoprofen (NSAIDs) that are not clinically important, so it is advisable to monitor the patient's clinical response [25].

Major severity is a drug interaction that can cause disability and cause effects that can threaten the patient's life. For example, the combination of amlodipine and simvastatin is one of the major interactions in most cases in this study, which were 11 cases. The interaction of these two drugs can cause a potential effect by increasing simvastatin levels in the blood. This process can lead to a risk of side effects, for example, liver damage and rhabdomyolysis, which involves the breakdown of skeletal muscle tissue. In some cases, rhabdomyolysis can cause kidney damage and even death [7]. Therefore, to prevent potential effects, it is recommended to limit the dose of simvastatin to 20 mg when combined with amlodipine [26].

Relationship between polypharmacy incidence and potential drug interactions

Table 5 describes the relationship between polypharmacy and potential drug interactions in geriatric patients with hypertension which the Chi-Square test has analyzed shows a significant relationship ($p = 0.000$). The table above also shows the OR (odds ratio) value of 8.793 with a lower limit of 3.870 and an upper limit of 19.979. This number implies that patients who received polypharmacy prescriptions had 8,793 times the risk of experiencing potential drug interactions compared to patients who did not receive polypharmacy prescriptions.

Table 4: Number of cases with potential drug interactions

Interaction type	Number of cases N = 258	%
Based on the interaction mechanism		
Pharmacodynamic	172	66,67
Pharmacokinetic	69	26,74
Unknown	17	6,59
Based on severity		
Minor	14	5,4
Moderate	227	88,0
Major	17	6,6

Table 5: Relationship between polypharmacy incidence and potential drug interactions

Type	Potential drug interactions		p-value	OR (min-max)
	Potential interaction n (%)	Non-potential interaction n (%)		
Polypharmacy	61 (87.1%)	9 (12.9%)	0.00	8.79 (3.870-19.98)
Non-polypharmacy	37 (43.5%)	48 (56.5%)		
Total	98 (100,0%)	57 (100,0%)		

*Chi-square test

Table 6: Relationship between polypharmacy incidence and severity of drug interactions

Type	Severity			Total n (%)	p-value
	Minor n (%)	Moderate n (%)	Mayor n (%)		
Polypharmacy	2 (3.3)	49 (80.3)	10 (16.4)	61 (100)	0,71
Non-polypharmacy	0 (0.00)	31 (83.8)	6 (16.2)	37 (100)	
Total	2 (2.0)	80 (81.6)	16 (16.3)	98 (100)	

*Fisher exact test

Relationship between polypharmacy incidence and severity of drug interactions

The relationship between the incidence of polypharmacy and the severity of drug interactions was analyzed using the Fisher Exact test to obtain a P-value of 0.714. There is no significant relationship between the incidence of polypharmacy and the severity of drug interactions.

Table 6 shows that moderate drug interactions are the most frequent for polypharmacy prescriptions and not. Moderate interactions are clinically significant, so the combination of these two drugs should be avoided and only used in special circumstances to avoid potential interactions. Furthermore, in improving the quality of patient treatment, drugs that have the possibility of major and moderate interactions should be avoided concurrently [58]. This result shows that interaction risk is higher than the benefits obtained. In addition, efforts is necessary to be made to minimize the occurrence of unwanted drug interactions to achieve treatment goals [28].

Several potential drug interactions can be prevented by pharmacists, including avoiding combinations of drugs that have a high risk, adjusting drug doses, giving pauses in drug administration if there are potential interactions, monitoring interactions by looking at the patient's clinical symptoms and with laboratory data, providing information about drug interactions, adverse effects to patients, screen drugs before they are given to patients, and minimize excessive drug combinations.

The endpoint in this study was patients discharge. The patient was declared healthy when he was discharged from the hospital. Sometimes, even though blood pressure has dropped, patients have to wait until they are declared healthy, especially for hypertensive patients with complications. In this study, all patients were discharged home with improvement.

This research has the advantage of having a detailed analysis of all aspects, both in terms of the type of interaction, the type of interaction, and the severity of the interactions that may occur. However, the data used is limited to hypertensive patients with a small sample size, so it cannot be generalized to all ages, diseases, and locations.

CONCLUSION

There is a fairly high interaction potential that is equal to 63.2%. Most potential drug interactions occur based on the mechanism of interaction, which are pharmacodynamics (66.67%), while based on severity, it is moderate (88%). There is a significant relationship between polypharmacy and potential drug interactions with a *p*-value = 0.00. In contrast, the relationship between polypharmacy and the severity of drug interactions did not have a significant relationship, with a *p*-value = of 0.00.

It is expected that pharmacists have an active role in monitoring the use of drugs that have the potential to root drug interactions by understanding potential interactions and notifying doctors if there are drugs that have potential interactions in patient prescribing. This action is expected to minimize unwanted risks to patients.

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ETHICAL APPROVAL

Ethical approval was acquired from The Research Ethics Committee of Medical Faculty, Andalas University No 646/UN.16.2/KEP-FK/2022

GUARANTOR

Faculty of Pharmacy Universitas Andalas is the guarantor of this research.

AUTHORS CONTRIBUTIONS

NF is the principal investigator in this study. NF design ideas and techniques in research. SW, and YOS collect and rewrite medical record data on worksheets. Furthermore, NF also performs data analysis and writes the manuscript.

CONFLICTING INTERESTS

The author(s) declare there is no conflict of interest regarding this manuscript.

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