

ANALYSIS OF POTENTIAL DRUGS INTERACTION ON ANTIHYPERTENSION DRUGS PRESCRIPTION IN COMMUNITY HEALTH CENTER OF SUKMAJAYA DISTRICT IN PERIOD OF JUNE-NOVEMBER 2015

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ABSTRACT

Objectives: Hypertension is a common disease around the world. Depending on the severity or the presence of other diseases, whether related or unrelated, additional drug therapy may be required to optimize treatment and to reduce the side effects of drugs. The use of drugs in large amounts may increase the risk of drug interactions. The purpose of this research was to evaluate the characteristics of hypertension patients, prescriptions, and potential drug interactions in hypertensive patients in the Sukmajaya Community Health Center from June to November 2015.

Methods: This research used a descriptive analytic method and the data were retrospectively obtained.

Results: The results were based on the analysis of 350 prescriptions of female (67.43%) and male (32.57%) patients, with the highest prevalence of hypertension occurring at the age of ≥ 55 years. Potential drug interactions were analyzed using Micromedex. The most frequent potential interaction resulted from the combined use of captopril and non-steroidal anti-inflammatory drugs. The most frequent mechanism of drug interaction was pharmacokinetics (51.06%). The chi-square test results showed a significant relationship between the number of prescribed drugs and potential interactions at a probability value of 0.0001 and an odds ratio of 5.940 (15.588-2.263).

Conclusions: With respect to interaction mechanism, pharmacokinetic (51.06%) was the most frequent and 61.70% of potential cases involved a moderate interaction risk.

Keywords: Antihypertensive, Potential drug interactions, Prescription.

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INTRODUCTION

Drug interactions may occur if the effects of one drug are altered by the presence of other drugs, herbal medicines, foods, beverages, or some chemicals [1]. The prevalence of drug interactions as a whole can reach 50-60% cases [2]. Basic-Vra *et al's* (2010) study of potential drug interactions analysis found a 51% prevalence of antihypertensive drug interaction cases, of which 60.9% involved pharmacodynamics mechanisms. In addition, studies in Indonesia on potential interactions between antihypertensive and other drugs in hypertensive patients in one community health center in Medan, found that 79.57% of drug combinations could potentially lead to drug interactions, including 45.71% of high severity [3].

Hypertension is the most prevalent non-infectious disease in Depok, affecting 53.9% of local population and representing 19,725 cases in 2013. This disease is the most commonly treated one in community health centers, especially in the age group of 45-75 years [4].

Therefore, based on this context, the authors of the present study aimed to analyze potential drug interactions with antihypertensive drugs prescribed in the Sukmajaya Community Health Center in Depok. This study is expected to contribute toward description of potential drug interactions with antihypertensive drugs and to serve as a reference for prescribing antihypertensive drugs in the Sukmajaya Community Health Center in Depok.

METHODS

A descriptive-analytic study was performed using a cross-sectional method. All data used in this study was secondary, that is, antihypertensive drug prescription records were retrospectively taken and analyzed from June to

November 2015. This study was conducted at the Sukmajaya Community Health Center from February to April 2016. The samples included antihypertensive drug prescriptions that met the inclusion criteria. The inclusion criteria are drug prescriptions containing antihypertensive drugs consisting of two or more drugs and the age of hypertensive patients ≥ 18 years. The sampling technique was proportionate stratified random sampling. This study samples were processed and analyzed using Micromedex®. Univariate analyses were performed to determine the number and type of drugs in a prescription, patient gender and age, potential drug interactions, and the mechanism of drug interaction as well as the potential degree of drug interaction severity.

RESULTS AND DISCUSSION

Subjects and population

Of the antihypertensive drug prescription data considered from June to November 2015, 2,741 prescriptions met the inclusion criteria. The number of samples examined based on the sample calculation was 350 prescriptions (Tables 1-3).

Overview of patient gender and age

The results of this study indicate that the number of female patients who received antihypertensive drugs (67.43%) was higher than that of male patients (32.57%). This result is in accordance with the hypertensive prevalence report in Basic Health Survey (RISKESDAS) in Indonesia in 2007 and 2013 carried out by the National Institute of Health Research and Development, wherein it was also reported that the prevalence of hypertension is higher in female patients than in male patients [5].

Female patients are more prone to hypertension than male patients based on their etiology and pathophysiology. As an example,

hypertension due to renal artery stenosis is more common in females than males. Other factors that cause hypertension in females are the use of oral contraceptives, pre-eclampsia, and vasculitis (inflammation of blood vessels) [6]. Furthermore, the risk of hypertension in females aged over 65 years is greater than males, and the severity of hypertension increases with increasing age [7].

This study also shows that the number of patient aged ≥ 55 years who received antihypertensive therapy (60.57%) is higher than patients aged < 55 years. This result is in accordance with a previous study that obtained a hypertensive prevalence rate of 66.66% in patients aged ≥ 55 years [8].

Patients aged ≥ 55 years face a 90% risk of developing hypertension according to the Joint National Committee 7 [9] as a result of the aging process, which leads to decreased physiological functioning of the body and causes individuals to become more prone to cardiovascular diseases such as hypertension. Hypertension in elderly patients is generally caused by arterial stiffness, neurohormonal and autonomic dysregulation, and renal insufficiency [7].

Overview of number and type of prescription drugs

Prescriptions with ≥ 4 types of drugs were more common (57.14% of all prescriptions) than prescriptions with 2-3 types of drugs (42.86% of all prescriptions). Drug combinations mostly reflected the treatment of hypertension in addition to other conditions. Other drugs prescribed beside antihypertensive drugs in the Sukmajaya Community Health Center included metformin, Vitamin B, antihistamine, antacid, paracetamol or PCT, and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, mefenamic acid, piroxicam, and diclofenac sodium.

Table 4 shows that types and combinations of prescribed antihypertension and the most prescribed drug for single prescriptions was amlodipine at Sukmajaya Community Health Center.

Amlodipine has been shown to be a well-tolerated antihypertensive drug, especially in elderly patients. Amlodipine tolerability has also been shown to be good or excellent in most patients. This is because amlodipine is slowly absorbed, and the side effects of vasodilation tend to be smaller than other CCB-group drugs. Amlodipine also has a low rate of metabolism in the liver and a longer half-life than other drugs, allowing effective blood pressure control with once-daily dosing [10].

Previous studies have also proven the effectiveness of amlodipine for decreasing blood pressure. Research conducted by Baharudin and Suwandi with 3 drugs comparison, namely, amlodipine, captopril, and

Table 1: Prescribed patients by gender

Gender	Patients n (%)
Male	114 (32.57)
Female	236 (67.43)
Total	350 (100)

Table 2: Prescribed patients by age

Age	Patients n (%)
< 55 years	138 (39.43)
≥ 55 years	212 (60.57)
Total	350 (100)

Table 3: Number of drugs in prescriptions

Number of drugs in prescriptions	Patients n (%)
2-3	150 (42.86)
≥ 4	200 (57.14)
Total	350 (100)

hydrochlorothiazide (HCT). The comparison showed that amlodipine could decrease blood pressure to 32.94/16.38 mmHg while captopril (29.16/11.83 mmHg) and HCT (27.05/9.35 mmHg) [11]. However, another study showed that amlodipine effectiveness in reaching target patient blood pressure is 100%, on the other hand, captopril and HCT had lower effectiveness in decreasing patients' blood pressure in 91% and 9%, respectively [12].

Overview of potential drug interactions

The analysis results from Table 5 show that of the 350 prescriptions analyzed, 39 prescriptions (11.1%) could have resulted in potential drug interactions. These interactions were more common in prescriptions containing ≥ 4 types of drugs. In addition, hypertension is a disease susceptible to drug interactions because they have to take their medication for lifetime and if they have other disease among their medication then the drug interaction may occur from other drug prescription [2]. These results concur with a study by Viktil *et al.*, which concluded that a higher number of drugs taken can lead to more drug therapy problems, including drug interactions [13].

The most common antihypertensive drug interaction occurred in association with captopril (44.74%), or in 17 cases, and with amlodipine (26.31%), or in 10 cases. These results are in accordance with Rumanda's study on the potential interaction of antihypertensive drugs in hypertensive patients at Medan Community Health Center, highlighting a 55% interaction potential for captopril and 40.71% for amlodipine [3].

The potential drug interactions in this study were derived from the analysis of the sample prescriptions using Micromedex, and the results are further detailed at following (Tables 6 and 7).

Amlodipine with simvastatin

Amlodipine can increase the effectiveness of simvastatin by decreasing the rate of simvastatin metabolism, resulting in an increase in the maximum level, and AUC value of simvastatin. At higher doses, there is

Table 4: Types and combinations of prescribed antihypertension drugs

Antihypertension drugs	Number
Single antihypertensive drug	
Amlodipine	297
Nifedipine	6
Captopril	20
Combination of 2 antihypertensive drugs	
Amlodipine + HCT	11
Nifedipine + amlodipine	1
Amlodipine + furosemide	9
Captopril + HCT	1
Amlodipine + propranolol	1
Combination of 3 antihypertensive drugs	
Nifedipine + amlodipine + HCT	2
Amlodipine + furosemide + HCT	1
Nifedipine + furosemide + amlodipine	2

HCT: Hydrochlorothiazide

Table 5: Potential drug interactions according to number of drugs in prescriptions

Number of drugs in prescriptions	Potential drug interactions		Total n (%)
	No potential interaction n (%)	Potential interaction n (%)	
2-3	145 (96.7)	5 (3.3)	150 (100)
≥ 4	166 (83)	34 (17)	200 (100)
Total	311 (88.9)	39 (11.1)	350 (100)

a risk of myopathy, including rhabdomyolysis. Monitoring of side effects is necessary. The use of other alternative medications or any reduction in the dose of simvastatin should not exceed 20 mg/day.

Amlodipine with domperidone

Simultaneous administration of amlodipine with domperidone can inhibit domperidone metabolism, which is mediated by CYP3A4, resulting in increased plasma concentrations of domperidone and an increased risk of QT prolongation. Case-control studies showed an increased risk of serious heart disease, including ventricular arrhythmias and sudden cardiac death, especially in domperidone doses greater than 30 mg/day and in patients older than 60 years.

Nifedipine with prednisone

Nifedipine is metabolized by the CYP3A4 enzyme. Concomitant use with CYP3A4 inducer (prednisone) will reduce AUC and C max to about 70%, so the effectiveness of nifedipine will decrease. Monitoring blood pressure is suggested. If prednisone treatment remains to be taken, then alternative antihypertensive treatments should be considered.

Nifedipine with aminophylline

The simultaneous use of nifedipine and aminophylline can alter serum aminophylline levels. Nifedipine alone cannot significantly alter antipyrine, showing that nifedipine does not affect the cytochrome P450 activity responsible for the metabolism of aminophylline. Any visible interactions between these two drugs may partly be due to competition between protein bonds.

Captopril with metformin

Captopril may affect insulin sensitivity, so combined usage with metformin may increase the hypoglycemic effect of metformin. Glucose monitoring is recommended, both during use and after captopril discharge.

Captopril with glibenclamide

Captopril may increase the glibenclamide effect through pharmacodynamics, specifically through a synergistic mechanism that increases the risk of hypoglycemia. Captopril can lower blood glucose by increasing insulin sensitivity, so the antidiabetic effect is increased and leads to greater hypoglycemic effects [14].

Captopril with antacid

Antacids may delay gastric emptying and increase the pH of the gastric lumen, causing a decrease in the absorption of alkaline drugs [1]. Antacid interactions with captopril may decrease captopril absorption, resulting in a reduction of captopril bioavailability to about 40%. If taken together, captopril should be taken 2 hrs before antacids are given.

Captopril with NSAIDs

The NSAIDs used in this study were ibuprofen, piroxicam, and mefenamic acid. The pharmacodynamics interactions with these drugs are antagonist. NSAID drugs can reduce the effects of vasodilators due to decreased prostaglandin synthesis in the kidney, thereby affecting fluid homeostasis, reducing antihypertensive effects, and possibly leading to renal dysfunction. Interactions should be monitored,

Table 6: Potential drug interactions in antihypertensive patients

Drug interactions	Severity degree	Mechanism type	n (%)
Amlodipine (5 mg and 10 mg) + simvastatin 10 mg	Major	Pharmacokinetic	7 (14.89)
Amlodipine 5 mg + domperidone	Major	Pharmacokinetic	3 (6.38)
Nifedipine 10 mg + prednisone	Major	Pharmacokinetic	1 (2.13)
Nifedipine 10 mg + aminophylline	Minor	Pharmacokinetic	1 (2.13)
Captopril 25 mg + metformin	Moderate	Pharmacodynamic	1 (2.13)
Captopril (12.5 mg and 25 mg) + glibenclamide	Moderate	Pharmacodynamic	2 (4.25)
Captopril (12.5 mg and 25 mg) + antacid	Moderate	Pharmacokinetic	4 (8.51)
Captopril (12.5 mg and 25 mg) + ibuprofen	Moderate	Pharmacodynamic	3 (6.38)
Captopril (12.5 mg and 25 mg) + piroxicam	Moderate	Pharmacodynamic	4 (8.51)
Captopril 12.5 mg + mefenamic acid	Moderate	Pharmacodynamic	1 (2.13)
Captopril 25 mg + allopurinol	Major	Unknown	1 (2.13)
HCT + captopril 12.5 mg	Moderate	Pharmacodynamic	1 (2.13)
HCT + piroxicam	Moderate	Pharmacodynamic	1 (2.13)
HCT + ibuprofen	Moderate	Pharmacodynamic	1 (2.13)
HCT + diclofenac natrium	Moderate	Pharmacodynamic	1 (2.13)
HCT + prednisone	Moderate	Pharmacodynamic	1 (2.13)
Furosemide + mefenamic acid	Moderate	Pharmacodynamic	2 (4.25)
Furosemide + piroxicam	Moderate	Pharmacodynamic	1 (2.13)
Furosemide + diclofenac natrium	Moderate	Pharmacodynamic	1 (2.13)
Ciprofloxacin + dexamethasone	Moderate	Pharmacodynamic	1 (2.13)
Glibenclamide + antacid	Minor	Pharmacokinetic	1 (2.13)
Antacid + mefenamic acid	Moderate	Pharmacokinetic	3 (6.38)
Vitamin C + antacid	Minor	Pharmacokinetic	1 (2.13)
Ciprofloxacin + diclofenac natrium	Moderate	Pharmacokinetic	1 (2.13)
Chloramphenicol + PCT	Minor	Pharmacodynamic	1 (2.13)
Domperidone + ranitidine	Major	Pharmacokinetic	2 (4.25)
Total			47 (100)

HCT: Hydrochlorothiazide

Table 7: Frequency of potential interactions in antihypertensive patients

Antihypertensive drugs	Name of drugs	Number of times drug prescribed	Number of potential drug interactions
Angiotensin-converting-enzyme inhibitor	Captopril	21	17
Beta Blocker	Propranolol	1	0
CCB	Amlodipine	324	10
	Nifedipine	11	2
Diuretic	HCT	15	5
	Furosemide	12	4

CCB: Calcium channel blocker, HCT: Hydrochlorothiazide

including the resulting antihypertensive effects, and kidney function should be periodically checked for signs of renal failure.

Captopril with allopurinol

The simultaneous use of captopril and allopurinol may cause hypersensitivity reactions and may also present risks for Stevens-Johnson syndrome and anaphylaxis. The interaction mechanism is unknown. However, to prevent the severity of such interactions, the hypersensitivity reaction should be monitored, and other alternatives should be used if needed.

HCT with captopril

The pharmacodynamics interaction between captopril and HCT is synergistic. The use of both captopril and HCT can simultaneously increase the effects of vasodilation and decrease the intravascular volume of blood, thus posing a risk of postural hypotension following the initial dose as well as acute hypotension and renal insufficiency. Blood pressure should be monitored during severe hypotension response for 4 hrs after initial dose.

HCT with NSAIDs

The NSAIDs used in this study were piroxicam, ibuprofen, and diclofenac sodium. The use of HCT with NSAID drugs simultaneously can decrease the production of renal prostaglandins, thereby decreasing the diuretic and antihypertensive effects. Monitoring of blood pressure, weight gain, and signs of renal impairment is required, including decreased urinary secretions and increased edema, and treatment may be necessary to reduce the side effects of drug interactions.

HCT with prednisone

Prednisone and HCT can interact through the mechanism of additive kaliuresis, thus raising the risk of hypokalemia, primarily as a result of strong glucocorticoid activity and arrhythmias.

Furosemide with NSAIDs

NSAID drugs and furosemide are antagonistic, and their interaction may decrease the effects of furosemide. NSAID drugs can specifically decrease the synthesis of renal prostaglandins, thereby reducing the diuretic and antihypertensive effects of furosemide.

Ciprofloxacin with dexamethasone

The simultaneous combination of ciprofloxacin and dexamethasone can result in an increase in the effects of each drug. Interaction effects may increase the risk of torn tendons (ruptured tendons). Combined use should be stopped if pain or inflammation occurs in tendons.

Glibenclamide with antacid

Simultaneous use of glibenclamide and antacids may increase the rate of glibenclamide absorption, which may lead to an increase in glibenclamide effects. Blood glucose monitoring for signs of hypoglycemia and reducing the dose of glibenclamide is required based on serum blood sugar.

Antacid with mefenamic acid

Magnesium hydroxide from antacids may increase the absorption of mefenamic acid, thus increasing the risk of side effects from mefenamic acid. Monitoring of possible antacid toxicity (e.g., nausea, vomiting, or depression) and appropriate dose adjustment are required.

Vitamin C with antacid

Vitamin C increases antacid levels ($Al(OH)_2$) by increasing their absorption in the gastrointestinal tract, possibly resulting in antacid toxicity, including seizures and coma.

Ciprofloxacin with diclofenac sodium

The use of ciprofloxacin and diclofenac sodium simultaneously can increase plasma concentrations of ciprofloxacin.

Table 8: Frequency of potential drug interactions by interaction mechanism

Interaction mechanism	n (%)
Pharmacokinetic	24 (51.06)
Pharmacodynamic	22 (46.81)
Unknown	1 (2.13)
Total	47 (100)

Table 9: Frequency of potential drug interactions by severity degree

Severity degree	n (%)
Major	14 (29.79)
Moderate	29 (61.70)
Minor	4 (8.51)
Total	47 (100)

Chloramphenicol with PCT

The simultaneous use of chloramphenicol and PCT leads to chloramphenicol toxicity, including hypotension, hypothermia, and vomiting.

Domperidone with ranitidine

Administration of ranitidine combined with domperidone may inhibit the domperidone metabolism mediated by CYP3A4, resulting in increased plasma concentrations of domperidone. Thus, ranitidine can increase the effects of domperidone and the risk of QT prolongation. Use with caution, as ranitidine may lead to serious heart disease, including ventricular arrhythmias and sudden cardiac death, especially for domperidone doses >30 mg/day and in patients older than 60 years.

Frequency of interaction mechanism type and interaction severity degree

The most frequent interaction mechanism in this study was pharmacokinetic (51.06%) (Table 8). This result concurs with Sivva *et al.*'s (2015) study on the assessment of drug interactions in hypertensive patients in one hospital in India, which also obtained more cases of pharmacokinetic (62.26%) than pharmacodynamic interactions. Drugs may limit the absorption of antihypertensive agents, alter their metabolism through either enzyme inhibition or induction, or change renal excretion. Furthermore, the antihypertensive response may be produced [1].

The results of this analysis are presented in Table 9, wherein the degree of interaction severity was most frequently moderate (in 61.70% of possible cases). This result is coherent with Sivva *et al.*'s (2015) study in which moderate interaction cases (84.90%) were much more common than major and minor interactions. Moderate interactions may lead to changes in patient clinical status, the need for additional treatment, or the prolongation of hospital stays [13].

CONCLUSIONS

Potential drug interactions in hypertensive patients taking antihypertensive drugs were identified in 39 prescriptions (11.1% of all studied prescriptions), with most interaction cases resulting from the combination of captopril with NSAIDs or of amlodipine drugs with simvastatin. With respect to interaction mechanism, pharmacokinetic (51.06%) was the most frequent and 61.70% of potential cases involved a moderate interaction risk.

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