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Original Article

POTENTIAL DRUG INTERACTIONS IN HYPERTENSIVE PATIENTS IN LIWA DISTRICT HOSPITAL, LAMPUNG BARAT, INDONESIA

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ABSTRACT

Objective: Patients with hypertension often suffer from other comorbidities, resulting in prescriptions of multiple drugs to treat the conditions. Multiple drug treatment is potentially associated with drug interactions. This aim of the study was to assess potential drug interactions in hypertensive patients in Liwa District Hospital.

Methods: The design of the study was cross-sectional. The prescriptions for in-patients with essential hypertension in the Internal Medicine Unit in Liwa District Hospital during April-December 2012 were collected. Potential drug interactions were analyzed with the Drug Interaction Facts version 4.0, and classified into minor, significant, and serious.

Results: A total of 60 hypertensive patients were included. They were prescribed 265 prescriptions, with a median total of 6 (range 1-21) drugs prescribed per prescription. There were 1616 potential drug interactions, with 6 (1-31) potential interactions per prescription. Most interactions (75.6%) were classified as significant. Serious potential interactions were most common in the combinations of diltiazem-amlodipine and spironolactone-potassium chloride, while significant potential interaction may occur most often with the combinations of calcium chloride-amlodipine and bisoprolol-amlodipine.

Conclusion: Numerous potential drug interactions might occur in hypertensive patients, and most interactions were significant in severity. The largest proportion of the interactions occurred between antihypertensive agents and other drugs.

Keywords: Drug interaction, Hypertension, Antihypertensive agent

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INTRODUCTION

Hypertension is still one of the most substantial challenges in healthcare in Indonesia. Based on Basic Health Survey 2013, the prevalence of hypertension was still high (25.8%), with evidence of inadequate control despite many available antihypertensive agents [1]. Increasing age, gender, educational level, body mass index, smoking, alcohol drinking, and underlying diseases are associated with the prevalence of hypertension [2]. It has also been suggested that different areas with different socioeconomic status might have different prevalence, awareness, treatment, and control of hypertension [3]. Hypertension itself is problematic since it is the risk factor of many cardiovascular diseases [4, 5], and may lead to myocardial infarction, stroke, renal failure, and death. Preventive efforts are crucial to decrease the risk of these cardiovascular diseases. Better blood pressure measurement can increase awareness towards hypertension, facilitate treatment, better hypertension control, and better outcomes [6].

Antihypertensive agents are available to reduce hypertension, along with lifestyle management. The Eighth Joint National Committee (JNC 8) has published a guideline on the management of hypertension, including the treatment. Based on the guideline, treatment with antihypertensive agents is started with one antihypertensive drug class (usually thiazide, angiotensin converting enzyme inhibitor [ACEI], angiotensin-II receptor blocker [ARB], or calcium channel blocker [CCB]), and the response will determine whether to add the dose or to add another antihypertensive drug class [7]. Often patients with hypertension will need more than one antihypertensive agent [7, 8]. A strategy to increase the efficacy, acceptability and adherence to antihypertensive drugs is needed, for example with the fixed-dose combination [9, 10].

Due to the fact that hypertension is one of the risk factors of many cardiovascular diseases, the older a patient gets, the more comorbidity the patient might have. The elderly patients have their own complex situation. Multiple comorbidities lead to the prescription of multi-drugs to treat these comorbidities, and this eventually leads to poly-pharmacy [11]. Therefore, not only hypertensive patients (particularly elderlies) would be prescribed many drugs for the treatment of hypertension itself, but also for treatment of the comorbidities [12]. There is a strong association between the number of drugs prescribed and potential drug interactions [13, 14].

There have been not many studies evaluating potential drug interactions in hypertensive patients in Indonesia. Therefore, this study was conducted with the aim to assess potential drug interactions in hypertensive patients in Liwa District Hospital.

MATERIALS AND METHODS

This cross-sectional study was conducted in the in-patients with essential hypertension in the Internal Medicine Unit in Liwa District Hospital during April-December 2012. All prescriptions for patients with essential hypertension in the Internal Medicine Unit were collected. Prescriptions for patients with secondary hypertension (renal hypertension, hypertension caused by drugs, endocrine disorder, and central nervous system disorder) were excluded.

Analysis of drug interaction was conducted using the Drug Interaction Facts version 4.0 from Wolters Kluwer Health (http:// reference. medscape.com/drug-interaction checker). The drug interactions were classified into three groups based on severity, namely, minor, significant, and serious (table 1).

Descriptive statistics were used to describe the characteristics of the patients and the number of potential drug interactions. Frequencies (or proportions) and medians with range were calculated for patient characteristics and drug interactions.

RESULTS

The present study included 60 hypertensive patients, who were prescribed 265 prescriptions. The median age of the patients was 53

y (range 32-90 y), and 60% of the patients were female. The median of drugs prescribed per prescription was 6 (1-21) (table 2).

Table 1: Drug interaction facts software classification scheme of the levels of severity of drugs interactions*

Level of severity	Description
1	Serious: an adverse effect can cause permanent damage or life risk.
2	Significant: an adverse effect can harm and treatment is required.
3	Minor: small or no clinical effect, with no treatment required.

* Drug Interaction Facts, version 4.0, 2006, by Wolters Kluwer Health. Electronic source: http://reference.medscape.com/drug-interactionchecker,

Table 2: Characteristics of patients in the study

Patient characteristic	Number of patients or value	%
Total number of patients	60	100
Total number of prescriptions	265	100
Median age (year), range	53 (32-90)	-
Sex		
Female	36	60
Male	24	40
Number of drugs prescribed per prescription, median (range)	6 (1-21)	-

Table 3 describes the frequency and classification of potential drug interactions found in the prescriptions. In the 265 prescriptions, there were 1616 potential drug interactions, with a median of 6 (1-31) potential drug interactions per prescriptions. The severity of the potential drug interactions was mostly significant (75.6%), while 4.4% and 0.8% were categorized as serious potential drug interactions and contraindications, respectively.

Table 3: Frequency, classification, and mechanisms of potential drug interactions

Potential drug interactions	No.	%
Number of potential drug interactions	1616	100
Number of potential drug interactions per prescriptions, median (range)	6 (1–31)	
Severity of drug interactions		
Contraindication	13	0.8
Serious	71	4.4
Significant	1222	75.6
Minor	310	19.2

Table 4: Description of potential drug interaction that is categorized as contraindication

Drug interaction (number of events)	Cases	Description	Level of severity
Ceftriaxone+calcium chloride (13)	8	Contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium. The administration of intravenous ceftriaxone and intravenous calcium needs to be separated by at least 48 h. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the intravenous infusion lines are thoroughly flushed between infusions with a compatible fluid.	Contraindication

Table 5: Description of potential drug interactions that are categorized as serious

Drug interactions (number of events)	Cases	Description	Level of severity
Diltiazem+amlodipine (14)	10	Diltiazem will increase the level or effect of amlodipine by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Diltiazem increases amlodipine exposure by 60%.	Serious
Diltiazem+bisoprolol (11)	9	Either increases the toxicity of the other by unspecified interaction mechanism. Can increase the risk of bradycardia.	Serious
Spironolactone+potassium chloride (14)	6	Spironolactone and potassium chloride both increase serum potassium.	Serious
Losartan+captopril (10)	4	Either increases the toxicity of the other by pharmacodynamic synergism. Dual blockade of renin-angiotensin system increases risks of hypotension, hyperkalemia, and renal impairment.	Serious
Ketoprofen+ketorolac (5)	4	Either increases the toxicity of the other by pharmacodynamic synergism.	Serious
Digoxin+bisoprolol (3)	3	Either decreases the toxicity of the other by unspecified interaction mechanism. Can increase the risk of bradycardia.	Serious
Aluminum hydroxide+digoxin (2)	2	Aluminum hydroxide will increase the level or effect of digoxin by increasing gastric pH. Applies only to oral form of both agents.	Serious

The potential drug interactions categorized based on the severity are summarized in table 4, 5, 6, and 7. The most common potential drug interaction categorized as contraindication was ceftriaxone and calcium chloride, because of the risk of precipitation of ceftriaxone-calcium. Serious potential drug interactions were most common in the combinations of diltiazem-amlodipine and spironolactone-potassium chloride. Diltiazem may increase serum amlodipine level by affecting CYP3A4, while the combination of spironolactone and potassium chloride will potentially increase potassium level. Significant potential drug interactions may occur most commonly with the combinations of calcium chloride-amlodipine and bisoprolol-amlodipine. Bisoprolol and amlodipine both will potentially increase antihypertensive channel blockade. Calcium chloride may decrease the effect of amlodipine. A minor potential drug interaction may occur most often with the combination of ranitidine and cyanocobalamin, due to the ranitidine effect in decreasing the serum level of cyanocobalamin by inhibiting gastrointestinal absorption.

Table 6: Description of potential drug interactions that are categorized as significant

Drug interactions (number of events)	Cases	Description	Level of severity
Calcium chloride+amlodipine (127)	52	Calcium chloride decreases effects of amlodipine by pharmacodynamics antagonism.	Significant
Calcium chloride+bisoprolol (72)	35	Calcium chloride decreases effect of bisoprolol by unspecified interaction mechanism.	Significant
Bisoprolol+amlodipine (92)	35	Bisoprolol and amlodipine both increase anti-hypertensive channel blocking.	Significant
Losartan+potassium chloride(68)	32	Losartan and potassium chloride both increase serum potassium.	Significant
Losartan+bisoprolol (76)	32	Losartan and bisoprolol both increase serum potassium. Mechanism: pharmacodynamic synergism. The risk of fetal compromise if given during pregnancy.	Significant
Bisoprolol+potassium chloride (69)	32	Bisoprolol and potassium chloride both increase serum potassium.	Significant
Ketorolac+potassium chloride (32)	16	Ketorolac and potassium chloride both increase serum potassium.	Significant
Potassium chloride+furosemide (39)	15	Potassium chloride increases and furosemide decreases serum potassium. Effect of interaction is not clear.	Significant
Bisoprolol+furosemide (19)	11	Bisoprolol increases and furosemide decreases serum potassium. Effect of interaction is not clear.	Significant
Ketorolac+bisoprolol (18)	10	Bisoprolol and ketorolac both increase serum potassium. Ketorolac decreases effects of bisoprolol by pharmacodynamic antagonism.	Significant
Captopril+potassium chloride (24)	10	Captopril increases levels of potassium chloride by decreasing elimination. The risk of hyperkalemia.	Significant
Bisoprolol+diltiazem (12)	10	Bisoprolol and diltiazem both increase anti-hypertensive channel blocking.	Significant
Aluminum hydroxide+bisoprolol (17)	10	Aluminum hydroxide decreases levels of bisoprolol by inhibition of gastrointestinal absorption. Applies only to oral form of both agents. These drugs need to be separated by 2 h.	Significant
Omeprazole+losartan (17)	9	Omeprazole will increase the level or effect of losartan by affecting hepatic enzyme CYP2C9/10 metabolism. May inhibit the conversion of losartan to its active metabolite E-3174. The importance of interaction not established; the individual therapeutic response needs to be monitored to determine losartan dosage.	Significant
Calcium chloride+diltiazem (14)	9	Calcium chloride decreases effects of diltiazem by pharmacodynamic antagonism.	Significant
Amlodipine+diltiazem (14)	9	Amlodipine and diltiazem both increase anti-hypertensive channel blocking.	Significant
Losartan+ketorolac (27)	8	Either increases the toxicity of the other. May result in renal function deterioration, particularly in elderly or volume depleted individuals. Ketorolac decreases effects of losartan by pharmacodynamic antagonism. NSAIDs decrease synthesis of vasodilating renal prostaglandins, and thus affect fluid homeostasis and may diminish antihypertensive effect.	Significant
Losartan+furosemide (21)	8	Losartan increases and furosemide decreases serum potassium. Effect of interaction is not clear.	Significant

Table 7: Description of potential drug interactions that are categorized as minor

Drug interactions (number of events)	Cases	Description	Level of severity
Ranitidine+cyanocobalamin (49)	23	Ranitidine decreases levels of cyanocobalamin by inhibition of GI absorption. Applies only to oral form of both agents.	Minor
Furosemide+calcium chloride (41)	15	Furosemide decreases levels of calcium chloride by increasing renal clearance.	Minor
Furosemide+thiamine (10)	7	Furosemide decreases levels of thiamine by increasing renal clearance.	Minor
Dexamethasone+calcium chloride (18)	7	Dexamethasone decreases levels of calcium chloride by increasing elimination.	Minor
Spironolactone+calcium chloride (14)	6	Spironolactone decreases levels of calcium chloride by increasing renal clearance.	Minor
Dexamethasone+amlodipine (11)	6	Dexamethasone will decrease the level or effect of amlodipine by affecting hepatic/intestinal enzyme CYP3A4 metabolism.	Minor
Omeprazole+cyanocobalamin (10)	5	Omeprazole decreases levels of cyanocobalamin by inhibition of GI absorption. Applies only to oral form of both agents.	Minor
Hydrochlorothiazide+ranitidine (8)	5	Hydrochlorothiazide will increase the level or effect of ranitidine by basic (cationic) drug competition for renal tubular clearance.	Minor

DISCUSSION

In this study, it was found that many potential drug interactions might occur in patients with hypertension, and most potential drug interactions were categorized as significant. The interaction might not only occur between antihypertensive agents themselves or between antihypertensive agent and other drugs, but also among other groups outside of antihypertensive agents, due to the concomitant diseases that usually occur in patients with hypertension in the age range included in this study (median age 53, range 32-90 y), as shown by the number of drugs prescribed per prescription (median number 6, range 1-21).

Several studies on potential drug interactions in hypertensive patients have been done. A previous study in India [15] showed that, from 899 hypertensive patients in the study, 87% were at risk of potential drug interactions, while in our study every patient was at risk of having potential drug interactions. In that study, 71.5% prescriptions were potentially having at least one drug interaction, with a total of 918 potential drug interactions. Another study was conducted in Croatia in elderly patients with arterial hypertension [16] and this study found 90.6% patients would potentially have clinically significant drug interactions, with the median number of significant potential drug interaction, was 4 (range 1-19). A study in Brazil also showed high potential drug interactions (93%) in patients with arterial hypertension and/or diabetes [17]. Another study in the United States of America suggested that potential drug interactions among hypertensive patients did not only occur in elderly patients, but also in younger patients. In that study, 23-48% patients were potentially had significant drug interactions [18].

The considerable number of potential drug interactions in this study warrants some concern, with a median of 6 potential drug interactions might occur per prescriptions, with most proportion was categorized as significant, which is similar to the results of Kothari's study that also showed that the potential drug interactions were mostly (95.4%) in significant category [15].

Potential drug interactions in hypertensive patients in this study most commonly might occur in the combination of antihypertensive agents with other drugs. There were also many cases with a combination of antihypertensive agents that were categorized as significant, such as the combination of bisoprolol-amlodipine, losartan-bisoprolol, bisoprolol-furosemide, bisoprolol-diltiazem, amlodipine-diltiazem, and losartan-furosemide. The previous study in India also showed that the most common combination that might lead to drug interaction in hypertensive patients were between antihypertensive agents, namely, atenolol-amlodipine and metoprolol-amlodipine [15]. The Croatian study suggested that antihypertensive agents were responsible for 51% potential drug interaction, with a combination of nonsteroidal anti-inflammatory drugs (NSAID) and antihypertensive agents and combination between ACEI and thiazide or loop diuretic as the most common potential drug interactions [16]. The study in Brazil indicated that the most frequent potential drug interaction was for the combination of acetylsalicylic acid-enalapril and glibenclamide-HCT [17]. Another study from India showed that potential drug interactions might occur in hospitalized patients who received amlodipine-atenolol combination or amlodipine-diclofenac combination [19].

These potential drug interactions not only would lead to failure of treatment but also might introduce the risk of adverse effects. Clinical and laboratory monitoring might be needed to assess these potential drug interactions, so that a dose adjustment, discontinuation, or another risk-modification strategy can be performed [20]. Computerised clinical decision support system can be used to prevent potential drug interactions. This system is increasingly used in hospitals to support evidence-based decision making by physicians and pharmacists [21-23].

There are several limitations of this study that need to be considered when interpreting the results. This study only assessed potential drug interactions but did not evaluate the actual adverse events occurred due to these potential drug interactions. However, it is not possible or ethical to assess the adverse events of a potential drug interaction without conducting an intervention to the potential drug interaction. Another limitation is that the list of drug interactions in the software is based on available evidence to date. Therefore, a drug that is available longer in the market will have more information on interactions compared to the newer ones, leading to more interactions occurred with older drugs compared to the newer drugs.

CONCLUSION

In conclusion, this study showed that many potential drug interactions might occur in patients hospitalized for hypertension, with the largest proportion of the interactions were significant in severity. Most interactions occurred between antihypertensive agents themselves and between the antihypertensive agent and other drugs. Serious potential drug interaction might occur most commonly with diltiazem-amlodipine combination or with spironolactone-potassium chloride combination; while significant potential drug interaction might occur most commonly with calcium chloride-amlodipine combination or with the bisoprolol-amlodipine combination.

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AUTHOR CONTRIBUTION

Erna Yanti planned the study and collected the data. Erna Kristin planned the study, conducted the analyses, wrote the drafts of the manuscript, as well as edited and agreed on the final version of the manuscript. Alfi Yasmina wrote the drafts of the manuscript and agreed on the final version of the manuscript.

CONFLICTS OF INTERESTS

All authors have no conflicts of interests to declare.

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