Potential Events of Drug Interactions among Elderly Hypertensive Patients in Surakarta Hospital

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Abstract: The use of antihypertensive drugs cannot be separated from the incidence of drug interactions. A study in 2017, showed that of 80 geriatric patients with hypertensive heart disease (HHD), 240 cases of potential drug interactions were found at Moewardi Hospital. This study aims to determine potential incidence of drug interactions in elderly hypertensive patients at Surakarta Hospital. This is an observational study using a cross-sectional method with retrospective data collection of patients in 2018 who were treated at Surakarta Hospital. The inclusion criteria were elderly patients more than 60 years, diagnosed with hypertension with or without comorbidities and receiving antihypertensive and non-antihypertensive drugs. Potential drug interactions were studied theoretically using Medscape.com. The data obtained were analyzed descriptively with cross-tabulation. The results of study were 86 patients who met the inclusion criteria. The theoretical potential for drug interactions was found in 98 cases from 505 cases. Pharmacodynamic drug interactions were most common in the use of bisoprolol with aspirin and furosemide with aspirin in 10 and 8 cases, respectively. The interaction between Valsartan and Atorvastatin as many as 6 cases with the type of pharmacokinetic interaction. It can be concluded that there are more pharmacodynamics than pharmacokinetic drug interactions.

1 INTRODUCTION

Hypertension is a challenge for Indonesia, because hypertension is a disease that is still often encountered in health services. The prevalence of hypertension is still quite high. The results of basic health research in 2018, the prevalence of hypertension aged 55-64 years was 55.2%, 65-74 years was 63.2%, and aged over 75 years was 69.5% (Riskesdas, 2018). At the age of 25 to 44 years the incidence of hypertension reaches 29%, at the age of 45 to 64 years it reaches 51%, and at the age of more than 65 years it reaches 65% (Warjiman, et al, 2020).

Hypertension is the most common non-communicable disease and continues to be a significant global health risk (Chobanian, et al, 2003). Currently, hypertension is a major problem in the world by causing 1.13 billion people to suffer from this disease and only 16.8% are receiving treatment (Bloch, 2016). In Indonesia, the prevalence rate of hypertension in 2013 was 25.8 percent and in 2018 it increased to 34.1 percent (Riskesdas,2013). Health data in Central Java in 2018 shows that hypertension still occupies the largest proportion of all non-communicable diseases reported at 57.10 percent (Riskesdas, 2018).

The incidence of hypertension will increase with age. Increasing age will cause an increase in blood pressure caused by an increase in arterial thickness and endothelial tissue dysfunction. This will cause a build up of collagen in the lining of the blood vessels which will cause the blood vessels to constrict, thereby reducing elasticity, becoming inelastic. This will cause the arteries to become stiff, blood will still be forced through these narrow blood vessels so that it will increase blood pressure. WHO estimates that there will be an increase in the incidence of hypertension in the proportion of the elderly in the world from 7% in 2020 to 23% in 2025. Hypertension in the elderly is related to sodium sensitivity. (WHO, 2015; Sigarlaki, 2006).

Research in 2015 said the prevalence of men was higher than women, but women had a higher level of alertness than men (Everett and Zajacova, 2015). But other studies say that women are more likely to have hypertension than men. Women are more at risk at the age of more than 45 years for hypertension, because before women experience menopause they have the

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hormone estrogen. This estrogen hormone will play a role in increasing HDL levels in the blood. At menopause, women will experience a decrease in the hormone estrogen, so it will reduce HDL in the blood and will increase LDL, this will cause atherosclerosis and increase blood pressure (Wahyuni and Eksanoto, 2013; Anggraini, et al, 2009).

Along with the increase in cases of hypertension, the use of drugs is an important element to achieved a good quality of life. When drug therapy is given to a patient, it is necessary to choose which drug to use first (first therapy). Treatment should be determined on the basis of appropriate evidence to reduce the risk of ADRs and drug interactions (Daskalopuolo, et al, 2015).

Drug interactions are a major problem among patients receiving multidrug therapy. WHO emphasizes that adverse drug reactions (ADR) and their effects can be significantly reduced by paying attention to people at risk for drug interactions (WHO, 2005). A drug interaction is defined as a qualitative or quantitative change in the effect of a drug due to the simultaneous or successive administration of different drugs. This may result in changes in the therapeutic effect and safety of one or both drugs. Drug interactions can occur pharmacokinetically (change in drug distribution to its site of action) or pharmacodynamically (change in target drug response) that require them to receive multidrug therapy (Osterhoutdt, et *al.,* 2011). The risk of drug interactions is potentially due to changes in the pharmacokinetics and pharmacodynamics of drugs with age (Mallet, et al, 2007). In 2017, a study by Prakoso showed that of 80 geriatric patients with hypertensive heart disease (HHD), 240 cases of potential drug interactions were found at Moewardi Hospital (Prakoso, 2019). The risk of drug interactions is very high among geriatrics due to the many comorbidities.

Based on previous research and the existing background, we aimed to determine the potential incidence of drug interactions in elderly hypertensive patients at the Surakarta City Hospital.

2 MATERIALS AND METHODS

This study is an observational study using a cross-sectional method with retrospective data collection obtained from the Surakarta City Hospital. The sample of this study was geriatric patients who received antihypertensives through outpatient installations for the period January 2018 - December 2018. Inclusion criteria were patients aged more than 60 years, diagnosed with hypertension with or without comorbidities, as well as patients receiving antihypertensive drugs and other non-antihypertensive drugs. While the exclusion criteria were patients who were not yet 60 years old and patients who did not receive antihypertensives. The object of research is data taken from medical records in the form of patient identity, diagnosis and treatment data including drug name, dose and frequency of use.

The data collected from medical records were studied theoretically for potential drug interactions using the Medscape database interactions checker and Stockley applications. In the Medscape drug interaction checker, there are several categories that are used to indicate the level of potential interaction, namely, minor (treatment can still be continued), significant (requires close supervision), and serious (it is recommended to change to alternative drugs). The data obtained were then analyzed descriptively with cross-tabulation. Data is displayed using tables and figures. Data were collected and entered into a Microsoft excel 2010 spreadsheet, and analyzed using SPSS for Windows version 16.0.

3 RESULT

This study obtained samples that match the inclusion and exclusion criteria as many as 86 patients. Patients consisted of 47.7% men and 52.3% women, shown in table 1. These results are in accordance with previous studies which said that elderly women were more at risk of developing hypertension than men because elderly women had reduced estrogen levels which had an effect on HDL levels in the blood

Table 1. Drug Use Data

Antihypertensive Drug Use	Frequency (Percentage)
Monotheraphy	34 (39,5)
Multidrug 2	33 (38,4)
Multidrug 3	17 (19,8)
Multidrug 4	2 (2,3)

Antihypertensive monotherapy was often used in 34 cases, while the rest underwent multidrug therapy. Antihypertensive monotherapy that is often used comes from the ARB group, namely Candesartan. As for the combination therapy, the ARB group with diuretics (Valsartan with furosemide or spironolactone.

This study found 98 cases of drug interactions from 501 cases of antihypertensive drug use in 86

patients. A total of 19.4% of cases found drug interactions in 86 patients who were obtained. Drug interactions are more common in pharmacodynamics than in pharmacokinetics. Pharmacodynamic drug interactions were 69.39%. Data on the incidence of drug interactions are shown in table 2. Interactions that occur with serious severity are 12.2%, while with minor severity are 21.4%, the rest is completed by monitoring the incidence of drug interactions.

Table 2: Drug Interaction Events on the Use of Antihypertensive Drugs

Drug Interaction	Frequency (Percentage)
Drug interactions occur	98 (19,4%)
Pharmacodynamics	68 (69,4%)
Pharmacokinetics	24 (24,5%)
Unknown	6 (6,1%)
Drug interactions do not occur	407 (80,6%)

4 DISCUSSION

Hypertension is less common in women than men, in those younger than 65 years, but is more common in elderly (65 years and over) women than men. In the United States, between 2011 and 2014, the prevalence of hypertension in women and men by age group was 8% versus 11% (20-34 years), 23% versus 23% (35-44 years), 33% versus 36% (45-54 years), 56% versus 58% (55–64 years), 66% versus 64% (65-74 years), and 81% versus 73% (≥75 years) (Benjamin, dd, 2017). In the research conducted, it was found that women had a higher incidence of hypertension than men.

After menopause in women, there is an increase in blood pressure which is influenced by the presence of estrogen and endogenous in the body, where there will be an increase in arterial stiffness, salt sensitivity, decreased endothelial nitric oxide production, and increased blood pressure.

Increased expression of angiotensin II receptors. This will lead to an increase in blood pressure and pulse pressure in postmenopausal women which are higher than men of the same age (old age) (Izumi, et al, 2007; Lobo, 2008; Steiner, 2003; Son, et al, 2017; Safar, 2005) Research from Korea says that after the age of 60, women are more likely to have hypertension and are less likely to maintain hypertension control than men of the same age range. Therefore, a sex-specific approach is recommended for effective blood pressure management (Choi et al., 2017).

Hypertension is more common in the elderly because of increased arteriolar and arteriolar wall stiffness, decreased baroreceptor sensitivity, increased responsiveness to sympathetic nerve stimulation, and changes in renal and sodium metabolism associated with aging (Pinto, 2007). Most hypertensive patients underwent multidrug therapy, only 39.5% of patients underwent monotherapy. This is in accordance with previous studies regarding the use of antihypertensive drugs (Busari, et al, 2010, Adejumo, et al, 2017). The class of antihypertensive drugs used in this study were ARBs, diuretics, Beta Blockers, CCBs, and ACE I. This is also in accordance with previous studies regarding the classes of antihypertensive drugs that are often used (Adejumo, et al, 2017; Olanrewaju, et al, 2011). ; Busari, et al, 2014; Busari, et al, 2010). The pattern of antihypertensive treatment is in accordance with the guidelines for managing hypertension by JNC 8. Diuretics are the first-line drugs for the management of hypertension according to the guidelines of JNC VII. Diuretics were prescribed more frequently which was comparable to studies conducted in several countries including India and the United States.

Good blood pressure control is usually easier to achieve with a single drug for patients with mild hypertension than in patients with moderate to severe hypertension, who often require multidrug therapy. The criteria for drug selection consider the patient's medical condition including the presence of comorbidities, the level of organ function, and age. Older patients usually respond to calcium channel blockers. Patients with DM, chronic kidney disease, and heart failure usually require ACEI to promote regression and prevent the development of this type of comorbidity (Baltazi et al., 2011). Combination treatment using antihypertensive agents from two different classes is useful and promising in controlling blood pressure in hypertensive patients (Herliany and Wahyuningsih, 2020).

The functions of the organs of metabolism and excretion of drugs determine the type and amount of drugs prescribed to individual patients. Measurement of organ function will help reduce adverse drug reactions and further organ damage due to accumulation of toxic drugs. However, drug dose, drug interactions, and side effects of drug reactions are not related to the magnitude of blood pressure control (Alahdal and Elberry, 2012; Karsch, et al, 2013, Abegaz, et al, 2017).

A drug interaction occurs when the effect of one drug is altered by the presence of another drug. Changes in the effect of these drugs can occur in pharmacodynamics (changes in drug effect

independent of concentration) and pharmacokinetics (changes in drug concentration). In this study, drug interactions were analyzed with the help of Medscape. In our study, the most frequent interactions were pharmacodynamic interactions of 69.4%. This is more common than pharmacokinetic interactions and interactions with unknown mechanisms. The results of this study are also in accordance with previous research, namely pharmacodynamic interactions are higher than pharmacokinetic interactions (Patel, et al, 2014; Subramanian, et al, 2018).

Interactions that occur are minor as much as 21.4% and there are also interactions that are serious as much as 12.2%. This is in accordance with other studies that found serious interactions between 3.6% and 29.6% (Sivva et al., 2015; Patel et al., 2014; Chelkeba et al., 2013).

Serious interactions that often occur in the pharmacodynamics of ramipril and aspirin use in 5 cases, the use of amlodipine with simvastatin with pharmacokinetic interactions in 3 cases, followed by the pharmacodynamic interaction between lisinipril and aspirin in 2 cases. The interaction between ramipril with aspirin and lisinopril with aspirin is a pharmacodynamic interaction which occurs by decreasing the synthesis of renal vasodilating prostaglandins. Then both will increase its toxicity if used together, especially in high-dose aspirin. The interaction between amlodipine and simvastatin will increase the serum level of simvastatin in the blood. Administration of this drug will increase the risk of myopathy or ramdomyolysis, so if it is used it is necessary to adjust the dose of simvastatin.

The most frequent interactions occurred in the interaction of bisoprolol with aspirin as many as 10 cases. This interaction is an interaction that can be completed by monitoring. The effect that occurs from this interaction is an increase in potassium levels in the blood. This also occurred in the interaction between furosemide and aspirin as many as 8 cases with interactions that occurred where aspirin would reduce blood potassium levels, while furosemide would reduce blood potassium levels. So it can be said that this interaction was completed by monitoring blood potassium levels in patients receiving furosemide with aspirin and bisoproplol with aspirin.

The drug that most often causes interactions with antihypertensive drugs is the use of aspirin. Aspirin inhibits the production of prostaglandins and can reduce the effectiveness of antihypertensives (Subramanian, et al, 2018). The results above can provide data on any drugs that interact with antihypertensive drugs. These data can be used as data on the prevalence of drug interactions in antihypertensive patients and can estimate the factors that influence the incidence of drug interactions. In addition, the data can also be used to implement or develop a procedure for handling drug interactions in hospitals, implementing appropriate interventions and other research studies can be carried out.

The limitation of this study lies in the software for analyzing drug interactions with medcape which can only estimate the potential for drug interactions. Data on therapeutic success cannot be seen in this study because the study is still limited to retrospective so that we cannot know the exact incidence of drug interactions that arise. Further research is needed on the potential drug interactions related to the success of therapy and how interventions can be carried out to reduce the incidence of existing drug interactions so as to reduce morbidity and mortality due to drug interactions.

5 CONCLUSIONS

Based on the results of this study, it can be concluded that the antihypertensive drugs found with monotherapy were 39.5%. The potential for serious drug interactions is 12.2%, while the minor ones are 21.4%. The incidence of drug interactions was more pharmacodynamic (69.4%) than pharmacokinetic (24.5%).

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