Jurnal Manajemen dan Pelayanan Farmasi (JMPF)
(Journal of Management and Pharmacy Practice)
ISSN-p : 2088-8139 | ISSN-e : 2443-2946
JMPF Vol 15(1) 2025: 73-78

Drug-Drug Interactions (DDIs) in Elderly Hypertensive Inpatients of the Academic Hospital of Universitas Gadjah Mada Yogyakarta

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ARTICLE INFO
Submitted : 22-11-2024
Revised : 16-01-2025
Accepted : 03-03-2025

Published : 31-03-2025

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ABSTRACT

Background: The prevalence of hypertension is higher among the elderly population. Elderly patients are considered a high-risk population for Drug-Drug Interactions (DDIs) due to multi-morbidity-related polypharmacy, age-related physiological changes, as well as pharmacodynamic and pharmacokinetic changes.

Objectives: This study conducted a drug use survey in the inpatient department of the Academic Hospital of Universitas Gadjah Mada Yogyakarta to assess Drug-drug interactions (DDIs) in individual prescriptions for elderly hypertensive patients.

Methods: This research employs an observational study design with a retrospective cohort approach. This study conducted at the Academic Hospital of Universitas Gadjah Mada Yogyakarta in January-December, 2021. The inclusion criteria for this study included patients diagnosed with hypertension, aged 60 years or older and those hospitalized.

Results: 120 prescriptions from 120 patients were collected from the medical records maintained by the Academic Hospital of Universitas Gadjah Mada Yogyakarta. This study identified 62 cases of Drug-Drug Interactions (DDIs), mainly due to drug interactions comprising 8 interactions unrelated to hypertension, and 54 related to hypertension. Three actual drug interaction events resulted in increased blood pressure, while the others were potential drug interactions. The most common occurrence of antihypertensive drug interactions in this study was at a moderate level of 54 events (87%).

Conclusion: From this study, it can be concluded that elderly patients are considered a natural high-risk population for DDIs. Each patient should be assessed individually based on their prescriptions, although in many cases, DDIs are unavoidable.

Keywords: Drug-Drug Interactions; Elderly; Hypertension; Inpatients

INTRODUCTION

Hypertension is a cardiovascular disease characterized by a persistent increase in arterial blood pressure. [1] The 2018 Basic Health Research (Riskesdas) indicates that the prevalence of hypertension diagnosed by doctors in Indonesia stands at 8.36%. The Special Region of Yogyakarta shows a higher prevalence of hypertension compared to the national figure, at 10.68%.[2] Based on the 2018 Riskesdas, the prevalence of hypertension is higher among the elderly population. [3] Elderly patients are particularly vulnerable to experiencing drug-related problems (DRPs) due to multi-morbidity-related polypharmacy, age-related physiological changes, as well as pharmacodynamic and pharmacokinetic changes. [4]

Polypharmacy, a condition marked by the concurrent use of five or more drugs per day, is one of the most common and direct effects of multimorbidity, particularly in older persons.[5] According to studies, polypharmacy affects 40-50% of all older persons. The use of evidence-based guidelines to prescribe drugs for individuals with various disorders can lead to complex and mutually exclusive treatment regimens. Concurrent use of many pharmaceutical medications can lead to major adverse events (SAE), poor adherence to therapy, and numerous

drug-drug interactions (DDIs) and drug-disease interactions (DDisIs).[6] Patients with Cardiovascular Disorders (CVD) are more likely to experience Drug-Drug Interactions (DDIs). Drug-drug interactions (DDIs) are a concern for patients taking several medications, but they are also a preventable cause of severe drug reactions. [7]

DDIs can have a variety of effects, including patient mortality and drug withdrawal. DDIs can change a drug's pharmacokinetics and/or pharmacodynamics, potentially leading to therapeutic failure or any adverse pharmacological event.[8] Pharmacokinetic interactions influence the disposition of drugs within the body and may transpire during the processes of absorption, distribution, metabolism, or elimination of the medications involved. Pharmacodynamic interactions among antihypertensive medications may result in synergistic or antagonistic effects on blood pressure reduction, potentially enhancing or diminishing adverse effects, contingent upon the specific agents implicated.[9] A retrospective study on potential drug-drug interactions (pDDIs) among ambulatory hypertension patients at Universitas Airlangga Hospital revealed that out of 704 patients, 53.98% were women and 46.02% were men. The study identified pDDIs in 89.06% (n = 627) of the patients, with a total of 1,354 pDDIs recorded. Among these, 89.4% (n = 1,210) were classified as moderate, while 9.8% (n = 133) were categorized as major.[10]

This study aims to determine drug interactions, especially Drug-Drug Interactions (DDIs) in elderly patients hospitalized at the Academic Hospital of Universitas Gadjah Mada Yogyakarta.

METHODS

Study design

This research employs an observational study design with a retrospective cohort approach. This study was conducted at the Academic Hospital of Universitas Gadjah Mada Yogyakarta in January-December, 2021.

Population and samples

The study subjects in this study consisted of elderly patients diagnosed with hypertension who were hospitalized at the Academic Hospital of Universitas Gadjah Mada Yogyakarta in January-December, 2021. The inclusion criteria for this study included patients diagnosed with hypertension, aged 60 years or older, and those hospitalized at the Academic Hospital of Universitas Gadjah Mada Yogyakarta during the specific period. The exclusion criteria encompassed patients with chronic kidney disease undergoing hemodialysis, patients experiencing hypertensive crisis, and patients receiving treatment in the Intensive Cardiac Care Unit (ICCU).

Study instruments and Data collection

Data in this study were sourced from the medical records maintained by the Academic Hospital of Universitas Gadjah Mada Yogyakarta. The prescriptions were collected and analyzed for Drug-Drug Interactions (DDIs) using DDI checkers. A data collection sheet is a structured tool used to systematically gather specific information from medical records in this study. The data collection process includes demographics (age, gender, length of hospital stay, and discharge status), medical history (hypertension diagnosis and comorbidities), medication data (details of antihypertensive drugs and other medications to assess interactions), laboratory and diagnostics data (blood pressure readings, renal function, and electrolytes).

Data Analysis

120 prescriptions from 120 patients were collected from the medical records maintained by the Academic Hospital of Universitas Gadjah Mada Yogyakarta. The prescriptions were collected and analyzed for Drug-Drug Interactions (DDIs) using DDI checkers such as Medscape databases, drugs.com databases, and Stockley's drug interactions. DDIs checkers were used to identify potential DDI and categorize them into mild, moderate, and severe categories. This study did not consider food, alcohol, or smoking-related interactions. In this study, drug interactions were checked using only one database per drug (Medscape, Drugs.com, and Stockley's Drug Interactions). The authors distinguished whether the interactions found were related or unrelated to hypertension by examining changes in the patient's blood pressure based on the patient's medical records while taking the medications.

RESULTS AND DISCUSSION

120 prescriptions from 120 patients were collected from the medical records. This study identified 62 incidents of Drug-Drug Interactions (DDIs), mainly due to drug interactions comprising 8 interactions unrelated to hypertension, and 54 related to hypertension. Three actual drug interaction events resulted in increased blood pressure, while the others were potential drug interactions. DDIs interactions can alter the pharmacokinetics

Table I. Drug-Drug Interactions in The Use of Antihypertensives in Hospitalized Elderly Patients

Categorization of drug-drug interactions based on severity	Frequency (n=62)	Percent (%)
Minor	0	0
Moderate	54	87
Major	8	13

Table II. Potential Drug-Drug Interactions (DDIs) That Do Not Affect Blood Pressure

No.	Drug Interaction Combination	Frequency (n=8)	Mechanism	Category
1	Furosemide/Metformin	1	Pharmacokinetic interactions	Moderate
2	Furosemide/Acarbose	1	Pharmacodynamic interactions	Moderate
3	Furosemide/Gentamicin	2	Pharmacodynamic interactions	Major
4	Furosemide/Gliquidone	1	Pharmacodynamic interactions	Moderate
5	Furosemide/Lantus Solostar (insulin glargine)	1	Pharmacodynamic interactions	Moderate
6	Diltiazem/ Methylprednisolone	1	Pharmacodynamic interactions	Moderate
7	Clonidine / Diphenhydramine	1	Pharmacodynamic interactions	Moderate

and/or pharmacodynamics of a drug which may leads to therapeutic failure or any adverse drug event.[8] DDIs are categorized based on their severity, reflecting the potential impact of the interaction. They are divided into three levels: major, where the interaction could be life-threatening or result in permanent harm; moderate, where the interaction might worsen the patient's condition or necessitate additional treatment or hospitalization; and minor, where the interaction is inconvenient but not medically significant.[11]

In Table I, the most common occurrence of antihypertensive drug interactions in this study was at a moderate level of 54 events (88%), while at a minor level, there were 0 events (0%) and a major level of 8 events (12%). A study conducted at Dr. Soedarso Regional General Hospital from January to June 2019 identified frequent occurrences of drug interactions with moderate severity, accounting for 61 cases (72%), and pharmacodynamic interaction mechanisms, observed in 79 cases (93%).[12] Moderate interactions that occur can cause a decrease in clinical status, requiring additional treatment such as hospitalization or referral.[13] Research conducted at dr. Soekardjo Tasikmalaya Regional General Hospital between April and May 2017 revealed that potential drug interactions at a moderate level occurred in 135 cases (57.2%) of the total 234 cases of drug interactions. [14]

In Table II, among the 8 non-hypertension-related interactions, the most common potential interaction that do not affect blood pressure involved antihypertensive and antidiabetic drugs, with four events. This study aligns with the results of a cross-sectional study conducted at a hospital in Jakarta, which reported potential drug interactions between antihypertensive and antidiabetic medications in 90.1% of patients, mostly involving pharmacodynamic interactions of moderate severity.[15] Furosemide, known for causing hyperglycemia, can reduce the efficacy of antidiabetic agents' therapeutic effects, necessitating glucose monitoring when used with antidiabetic drugs.[16]

Based on Table II, the potential for antihypertensive drug interactions with other drugs with a major severity level was the interaction between furosemide and gentamicin. Interaction between furosemide (loop diuretic) and gentamicin (aminoglycoside group) occurred in 2 cases in this study. The mechanism of interaction between the two drugs is that furosemide can increase the adverse/toxic effects of aminoglycosides (nephrotoxicity and ototoxicity). Monitor for toxic effects of aminoglycosides (i.e., ototoxicity or nephrotoxicity) if loop diuretics are started together with gentamicin.[16] Following the administration of antibiotic medication, a comprehensive assessment needs to be conducted. [17]

In Table III, among the 54 hypertension-related interactions, the most common potential interaction that affects blood pressure involved antihypertensives and NSAIDs, with 43 events. NSAIDs reduce the effectiveness of antihypertensive medications by inhibiting prostaglandins. However, the impact on blood pressure varies among different antihypertensives, depending on the extent of prostaglandin (PG) inhibition and the specific

Table III. Potential Drug-Drug Interactions (DDIs) That Affect Blood Pressure

No.	Drug Interaction Combination	Frequency (n=54)	Mechanism	Category
1	Candesartan / ketorolac	8	Pharmacodynamic interactions	Moderate
2	Candesartan / Spironolactone	1	Pharmacokinetic interactions	Major
3	Candesartan / Aspirin	1	Pharmacodynamic interactions	Moderate
4	Candesartan/Potassium chloride	2	Pharmacodynamic interactions	Major
5	Candesartan / Mefenamic acid	1	Pharmacodynamic interactions	Moderate
6	Candesartan/Enoxaparin sodium	1	Pharmacodynamic interactions	Moderate
7	Candesartan / heparin sodium	1	Pharmacodynamic interactions	Moderate
8	Valsartan / Mefenamic acid	1	Pharmacodynamic interactions	Moderate
9	Valsartan / Flunarizine	1	Unknown	Moderate
10	Valsartan / ketorolac	1	Pharmacodynamic interactions	Moderate
11	Telmisartan / Potassium chloride	1	Pharmacodynamic interactions	Major
12	Telmisartan / heparin sodium	1	Pharmacodynamic interactions	Moderate
13	Telmisartan/ketorolac	1	Pharmacodynamic interactions	Moderate
14	Irbesartan / ketorolac	1	Pharmacodynamic interactions	Moderate
15	Furosemide/ Methylprednisolone	1	Unknown	Moderate
16	Hydrochlorothiazide/methylprednisolone	1	Unknown	Moderate
17	Amlodipine / Diclofenac	2	Pharmacokinetic interactions	Moderate
18	Amlodipine / Mefenamic acid	1	Pharmacokinetic interactions	Moderate
19	Amlodipine/ Antalgin (Metamizole)	1	Pharmacodynamic interactions	Moderate
20	Amlodipine / Flunarizine	1	Unknown	Moderate
21	Amlodipine / Ketorolac	15	Pharmacokinetic interactions	Moderate
22	Bisoprolol / Ketorolac	1	Pharmacodynamic interactions	Moderate
23	Bisoprolol / Fentanyl	1	Pharmacodynamic interactions	Moderate
24	Nifedipine / ketorolac	3	Pharmacodynamic interactions	Moderate
25	Nifedipine / Mefenamic acid	1	Pharmacodynamic interactions	Moderate
26	Captopril / ketorolac	1	Pharmacodynamic interactions	Moderate
27	Furosemide / Ketorolac	2	Pharmacodynamic interactions	Major
28	Furosemide / Diclofenac	1	Pharmacodynamic interactions	Moderate

mechanisms of action of each antihypertensive drug. Thus, highlighting the need for blood pressure monitoring when these drugs are used together.[16] The risk of hyperkalemia may be enhanced potentially in patients receiving a RAS blocker and potassium-sparing diuretics, heparins or an NSAID, potassium supplements, adrenergic betablockers, antifungal agents, trimethoprim, calcineurin inhibitors, concomitantly.[18]

In another study, synergistic nephrotoxicity was not observed with short-term NSAIDs with RAS-I treatment in the absence of concomitant diuretics. [19] Renin–angiotensin system inhibitors (RASI) inhibitors are a group of drugs that act by inhibiting the renin-angiotensin system (RAS) and include angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin-receptor blockers (ARBs).[1]

Based on Table III, the potential for antihypertensive drug interactions with other drugs with a major severity level was the interaction between ARBs and potassium. The interaction between ARBs and potassium supplements may increase the hyperkalemic effects of ARBs. This interaction is most likely the result of the additive effects of aldosterone suppression in patients receiving ARBs which may increase potassium retention and potassium supplementation.[16] A retrospective cohort study conducted at Nihon University Hospital in Japan revealed that patients treated with ARBs had higher serum potassium levels (0.05 mEq/L, p=0.02) compared to those receiving CCB therapy.[16,20] Monitor therapy for signs and symptoms of hyperkalemia during concomitant use of ARBs and potassium supplements.[16]

In Table IV, this study identified three actual drug interaction events resulted in increased blood pressure. The actual drug interactions occurred in the use of drug combinations between Candesartan/Ketorolac, candesartan/Enoxaparin sodium, and Amlodipine/Ketorolac, each of which occurred in 1 case. Drug interactions

Table IV. Actual Drug-Drug Interactions (DDIs) That Affect Blood Pressure

No.	Drug Interaction Combination	Frequency (n=3)	Mechanism	Category
1	Candesartan/Ketorolac	1	Pharmacodynamic interactions	Moderate
2	Candesartan/Enoxaparin sodium	1	Pharmacodynamic interactions	Moderate
3	Amlodipine/Ketorolac	1	Pharmacokinetic interactions	Moderate

that occur may be due to polypharmacy and decreased organ function in geriatric patients, so in this case, monitoring of drug interaction events is necessary. NSAIDs and antihypertensives were engaged in all three occurrences of the actual interaction. NSAIDs reduce the effectiveness of antihypertensive medications by inhibiting prostaglandins. However, the impact on blood pressure varies among different antihypertensives, depending on the extent of prostaglandin (PG) inhibition and the specific mechanisms of action of each antihypertensive drug. Thus, highlighting the need for blood pressure monitoring when these drugs are used together.[16]

This study is consistent with research conducted at Dr. Soedarso Pontianak Regional Hospital from January to June 2019, which found that there were changes in blood pressure in patients with geriatric hypertension inpatients, both decreases and increases, as a result of antihypertensive drug interactions.[21,22] Research conducted at Dr. Soedarso Regional General Hospital between January and June 2019 discovered drug interactions in elderly hypertensive inpatients was a combination of amlodipine dan ketorolac, amlodipine dan metformin, valsartan dan acetylsalicylic acid, and also valsartan and atorvastatin.[12] Research conducted at dr. Soekardjo Tasikmalaya Regional General Hospital between April and May 2017 revealed drug interactions in elderly hypertensive inpatients was a combination of furosemide and paracetamol, digoxin and ramipril, aspirin and spironolactone, and spironolactone and potassium chloride. [14]

The limitations of this study were that this research conducted in a single hospital or region may not reflect the variability in prescribing practices or patient populations in different geographical or healthcare settings, and this study's findings depend on the reliability and comprehensiveness of the interaction databases or tools used (Medscape, Drugs.com, and Stockley's Drug Interactions). These databases might not include all possible DDIs or may differ in their classification.

CONCLUSION

This study identified 66 cases of Drug-Drug Interactions (DDIs), mainly due to drug interactions comprising 8 interactions unrelated to hypertension, and 58 related to hypertension. Three actual drug interaction events resulted in elevated blood pressure, while the others were potential drug interactions. From this study, it can be concluded that elderly patients are considered a natural high-risk population for DDIs. Each patient should be assessed individually based on their prescriptions, although in many cases, DDIs are unavoidable.

STATEMENT OF ETHICS

Ethical approval for this research was granted by the Faculty of Medicine, Public Health and Nursing Research Ethics Commission at Universitas Gadjah Mada, Yogyakarta under approval number KE-FK-0500-EC-2022.

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