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Does Hypertensive Patients are More Susceptible to the Risk of Drug-Drug Interactions?

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Abstract

Drug-Drug Interactions (DDIs) are the main problem among patients treated with multidrug therapy. Cardiovascular Diseases (CVD) consider the main cause of all morbidities and mortalities in universal. The major cause of CVDs death is hypertension. Clinical trials have reported that the treatment of hypertension minimizes CVD cases and all reason of mortality. Hypertensive patients are especially suspectable to DDIs due to their age, polypharmacy, comorbid conditions, long hospital stay and the presence of a drug therapy for other comorbid conditions that arise as a complication of long-term hypertension. This article reviews different case studies evaluating DDIs in hypertensive elderly patients with polypharmacy. The most generally prescribed drug group that observed mostly in all case studies are: antihypertensives, Non-Steroidal Anti-Inflammatory Drug (NSAIDs), antidiabetics, antibiotics, antihistaminic, cardiac glycosides, calcium supplements, antimicrobial, Central Nervous System (CNS) depressant, thiazide diuretics, Lipid lowering drug, antigout, anticoagulants, analgesics, antibacterial and antianxiety. DDIs checker tool used in different case studies are REAX-Micromedex, Beers Criteria, Lexi-Interact software and Medscape checker software. The common interacting drug pairs among the antihypertensive drugs were atenolol-amlodipine, furosemide-telmisartan, furosemide-enalapril, furosemide-atenolol and metoprolol-amlodipine. Both pharmacokinetics and pharmacodynamics type of DDIs were found in most cases but with different rates. The severity of DDIs was mainly significant and moderate. The prevalence of DDIs was differ from case to case depend on drug pair used and clinical disorder in each case. The majority of DDIs can be addressed through the dosage adjustment and lab monitoring of patient. This is particularly significant in the case of accompanying medication with various groups of antihypertensive drugs.

Keywords: Drug-Drug interaction, Hypertensive, Cardiovascular diseases, Elderly patients, Multidrug therapy, Polypharmacy, DDI checker tool.

Abbreviations: DDIs-Drug-Drug Interactions, CVD-Cardiovascular Diseases, NSAIDs-Non-Steroidal Anti-Inflammatory Drugs, CNS-Central Nervous System, WHO-World Health Organization, ACE-Angiotensin-converting enzyme, ARBs-Angiotensin Receptor Blockers, CYP3A-Cytochrome P450, BB-Beta blocker.

Introduction

Drug-Drug Interactions (DDIs) are the main problem among patients used multidrug therapy. The World Health Organization (WHO) asserts that adverse drug reaction and its effect can be reduced significantly by the achievement of attentive to the people at the risk of DDIs [1]. Drug interaction can be defined as the quantitative or qualitative change of the impact of a drug by the concurrent administration of different drug. This may lead to changes in the therapeutic effectiveness and integrity of the drugs.

Drug interactions can be due to pharmacokinetics interaction that result in the change of drug delivery to its site of action or pharmacodynamics interaction that result in response modification of drug objective [2]. However, the possibilities of DDIs may increase day by day because of simultaneous use of many drugs as well as new pharmacological agents are introduced. So, the awareness and knowledge about DDIs may provide the framework for protection [3]. Cardiovascular Diseases (CVD) consider the main cause of all morbidities and mortalities in universal. Moreover, it is predicted that the worldwide CVD will be expanded by almost 75% by the year 2020 [4]. The major cause of CVDs death is hypertension. Hypertension is considered the major adjustable risk factor for CVD and early mortality in US and worldwide [5-9]. Observational studies have revealed solid and positive relation between blood pressure and risk of CVD and mortality [10,11]. However, clinical trials have reported that the treatment of hypertension minimizes CVD cases and all reason of mortality. It was observed in India that hypertension is immediately responsible for 57% of all stroke and 24% of all coronary heart disease mortalities [12]. Every year a number of antihypertensive drugs are introduced and a new potential interaction between medications will increase day by day, and this will lead an increase in the risk of hospitalization and healthcare cost.

Hypertensive Patients and the Risk of DDIs

Hypertensive patients are especially suspectable to DDIs as a consequent to their age; polypharmacy, comorbid conditions, and long hospital stay [13]. In addition to the presence of a drug therapy for other comorbid conditions that arise as a complication of long-term hypertension, like congestive cardiac failure, diabetes mellitus, coronary artery disease, and chronic kidney disease which may contribute for increasing the risk of DDI [14]. However elderly patients are at higher risk for DDIs because they are probably having many

diseases and polypharmacy that generally occur with long term of disease condition and change physiology. Moreover, many studies are reported that the age more than 60 is an independent risk factor for DDIs [15]. Moreover, there is a relationship between the number of prescribed drugs and the risk of DDIs. Generally, the prevalence of DDIs in patients taking 2 to 4 drugs is 6%, in patients taking 5 drugs is 50% and in patients taking 10 drugs is nearly 100% [16].

The potential DDIs for a specific antihypertensive drug changes with the person, the disease being treated, and the length of exposure to other drugs. Many Studies had shown that DDIs are more prevalent in the old age group>60 years [17,18]. The potential reason could be due to decrease in the renal and hepatic functions, further comorbidities, and the drugs prescribed for every clinical disorder [19]. Many studies were performed to detect and evaluate DDIs among hypertensive elderly patients treated with multidrug therapy. This article will demonstrate different case studies estimating DDIs in hypertensive elderly patients with polypharmacy.

Case 1

A study by Divya, et al. was designed to estimate the extent and type of clinically important DDIs in hospitalized hypertensive patients in India for the estimation of reaction features, result, and management [20]. REAX-Micromedex system and Medscape multidrug interaction checker tool were used to assess DDIs [20]. Most of the patients were in the age group of 50-60 years, and the most generally prescribed types of drugs are antihypertensives, NSAIDs, antidiabetics, antibiotics, anti-asthmatics, cardiac glycosides and calcium supplements.

Out of drugs prescribed 38.09% were antihypertensives and the beta blockers were dominant 50.7%. This was in agreement with the study performed by Dinesh KU, et al. also showed that the most commonly prescribed types of drugs to elderly hospitalized hypertensive patients were antihypertensives, NSAIDs, antidiabetics, antihistamines, antidepressants, and proton pump inhibitors and demonstrates that 50% of interacting drugs were anti-hypertensives [21]. In Divya, et al. study generally the most common drugs responsible for DDIs was insulin 34% followed by Metoprolol 18.9%, Torsemide 15.1% and Hydrochlorothiazide 15.1%.

They notice out of the DDIs 84.9% were significant and moderate in severity, therapy monitoring and dosage regulation is needed. The nature of drug interaction was reported 62.3% of DDIs were pharmacokinetic and 37.7% were pharmacodynamic interactions. About 32.07% of DDIs were delayed type, like in the case of Atenolol and Insulin, so patients counseling is required for patient at risk for undergoing these DDIs [20]. The overall incidence rate of DDIs was found to be 21.14% and the most commonly interacting pairs were Ciprofloxacin-Insulin followed by Atenolol-Insulin, Metoprolol-Insulin [21].

Case 2

A cross-sectional study carried out by Rajat Kumar, et al. at tertiary care teaching hospital in central India among elderly hypertensive patients undergoing multidrug therapy [16]. They find the potential DDIs among medications prescribed by using Beers Criteria which is a considerable method used for assessment suitability of prescribing in elderly. In this study, potentially inappropriate medicines prescribed were 1.98% of total prescribed drugs in elderly patients [16]. The most common drug groups prescribed to patients in this study were calcium channel blockers, cardiac glycosides, NSAID, antihypertensive and antimicrobial agents. In this study 67.3% potential DDIs were noticed among elderly hypertensive patient. Most common DDIs were of moderate grade 50.6% Mild DDIs were 8.6% and severe DDIs were 7.9%. Most common potential inappropriate medicine used was spironolactone followed by diltiazem, diclofenac, olanzapine, metoclopramide, digoxin, insulin and isopto-hyoscine in the study population [16].

Case 3

A prospective study performed by Vesna Bacic-Vrca, et al. was carried out at three community pharmacies in Croatia [22]. The study involved elderly outpatients 65 or older, treated for arterial hypertension and received two or more drugs. The potential DDIs were identified by Lexi-Interact software. In this study (83.3%) of interactions had clinical significance C (that monitor therapy due to the presence of significant interaction). The most common potential interaction was between NSAID and antihypertensive drugs, as 33% of patients included in the study experience osteoarthritis that treated with NSAID therapy.

In this study more than one antihypertensive drug were needed and most DDI between antihypertensives had clinical significance category C (monitoring therapy is required). However, the most common interaction in this group was the interaction between ACEI and thiazides or loop diuretics as the majority of patients in this study were treated with these classes of antihypertensive drugs [22]. Radosevic, et al. detect that the most common potentially harmful drug combination in hospitalized patients was an ACEI with a potassium supplement [23].

Loop diuretics are more potent than thiazides, and more often cause hypovolemia and hyponatremia. That is why the risk of pharmacodynamics interactions is higher when loop diuretics are combined with other antihypertensive drugs compared to thiazides. In this study more than half of patients treated with benzodiazepines. Elderly patients are sensitive to this medication due to pharmacodynamics and pharmacokinetic changes.

The consequent use of other drug that effects the CNS such as opioids, antidepressant, antipsychotics, may have additive depression of its action. Moreover, some classes of drugs such as calcium antagonists may affect the metabolism of benzodiazepines. All these factors may change the response to these drugs leading to adverse drug reaction. However, these potential DDIs in elderly patients with arterial hypertension can be controlled through laboratory monitoring of patients or by dosage adjustments of one or both agents.

Case 4

This is a prospective, cross-sectional study by Ansha, et al. was preceded among the hypertensive patients in medicine department for both outpatient and inpatient over the period of three months in a tertiary care hospital in India [19]. The DDIs were analyzed with the help of Medscape interaction checker, the majority of study population 56% was in the age group of 40-60 years. DDIs were identified and majority of them were significant 85.36%. However, no serious interactions were identified [19]. This study observed that 37.3% of the DDIs are pharmacodynamic in nature followed by 28.7% pharmacokinetic interactions, this is in agreement with a study carried out by Patel, et al. [24].

The drug groups that involved in interactions are antihypertensive drugs, calcium supplements, cardiovascular drugs, NSAIDs, antibiotics, and oral hypoglycemic, which are in similar to other studies [25,26]. However, this study recorded that 30% of DDIs occurred between antihypertensive drugs and calcium supplements followed by 28.4% within the antihypertensive drugs [19]. The common interacting drug pairs among the antihypertensive drugs were atenolol-amlodipine, furosemide-telmisartan, furosemide-enalapril, and furosemide-atenolol similar to Chelkeba, et al. study [26].

Among the antihypertensives interacting with other cardiovascular drugs, aspirin was most frequently involved in DDI. These drug combinations were the common interactions identified: Aspirin/enalapril, aspirin/spironolactone, aspirin/carvedilol, aspirin/atenolol, aspirin/furosemide, and aspirin/metoprolol. Aspirin blocks the prostaglandins production and could decrease the effectiveness of antihypertensives.

In this study, the following drug pairs result in DDIs, digoxin/enalapril, digoxin/spironolactone, and digoxin/ furosemide. Spironolactone could increase digoxin concentration by reducing its clearance [26]. Among the interaction between the antihypertensive drugs and NSAIDs, frequent DDI was between enalapril and diclofenac. Diclofenac is a cyclooxygenase inhibitor will decrease the activity of enalapril by inhibiting the prostaglandin vasodilating effect of Angiotensin-Converting Enzyme (ACE) inhibitors and also causes an increased risk of renal function impairment through compromising renal hemodynamics [27].

This study observed DDIs between antihypertensives and other class of drugs, amlodipine/fluconazole, amlodipine/metronidazole and enalapril/glyburide, the reason for this interaction, fluconazole a Cytochrome P450 (CYP3A) enzyme inhibitor, causes inhibition of amlodipine metabolism leading to increased risk of hypotension [28]. Moreover, the administration of ACE with the sulfonylureas may increase the insulin sensitivity by vasodilatation and increase the risk of hypoglycemia [29].

Case 5

Other study performed by Nitin Kothari, et al. an observational cross section study proceeded in a tertiary care teaching hospital of central Gujarat, India, to detect potential DDIs among hypertensive patients with average age 63.50 years [30]. The potential DDIs were detected with the help of Medscape drug interaction checker software [31]. It was found that 71.50% of prescriptions have at least one DDIs. This study found that the most frequent drug pairs that produce DDIs are atenolol-amlodipine (136) followed by metoprolol-amlodipine (88). The next common pairs were aspirin-atenolol (56), aspirin-enalapril (52) and metformin-hydrochlorothiazide (48) [30]. Serious type of DDIs was showed between ACE inhibitor and Angiotensin Receptor Blocker Drugs (ARBs).

In this study most common drug group involved in potential DDIs was the beta blocker 46.07% and diuretics 32.08% [30]. This study found that the most type of DDIs were 4.8% pharmacokinetic and pharmacodynamic 55.23% type. However, 72.2% of pharmacodynamic DDIs were of synergistic type and 27.8% were of antagonistic type [30]. The common prescribed drug pair in this study was beta blocker- amlodipine with adverse effect on plasma renin activity so it's helpful for the patient to check any adverse drug reaction [32]. This study found aspirin was the most common drug causing DDIs, this is in agreement with study conducted by Bista D, et al. because aspirin increases serum potassium level and serum potassium level is changed by most all antihypertensive medications including ACE inhibitors, ARBs, Beta blocker (BB) and diuretics [33].

Case 6

A retrospective study was done by Sagar, et al. at general medicine ward of secondary care hospital in Secunderabad/ India for a period of 9 months for the detection of DDIs in prescriptions containing antihypertensive drugs which was prescribed [34]. This study found 20.5% of the prescriptions has drug interactions with antihypertensive agents. These antihypertensive agents are having the interactions with different classes of drugs like antifungal drugs, anticoagulant drugs, analgesics, antihypertensive drugs, anxiolytics, antigout drugs, antibacterial drugs, diuretics, and lipid lowering drugs. Drug interaction prescriptions were analyzed and founded the 26 different types of DDIs with antihypertensive agents 4 major interactions and 15 moderate interactions were founded [34].

The most drug that interacting with maximum of other drugs was found to be amlodipine (Enalapril, Aspirin, Fluconazole, Atenolol, Nebivolol, Ramipril, Calcium Carbonate, Furosemide, and Indapamide) and combination which is repeated mostly was amlodipine and atenolol. These drug interactions can be effectively controlled by dose adjustments, regular monitoring of blood pressure, renal function, electrolytes, careful use of combination of drugs, clinical monitoring of the patient, and laboratory observation of the patient mostly in the cases of major and moderate drug interactions.

Conclusion

Multi-drug therapy can be avoided by sharing treatment objective and plans. For the improvement of drug integrity in hypertensive patients, suitable prescribing may be more significant than just decreasing the number of prescribed drugs. The majority of DDIs can be addressed through the dosage adjustment and lab monitoring of patient. This is particularly significant in the case of accompanying medication with various groups of antihypertensive drugs. However, in other cases changes in drug therapy should be considered.

Medication review programs should be concentrated and implemented in hospitals to prevent life threatening DDIs and ensuring better patient care. The knowledge about the drug interaction may render the frame for prevention. Computer-based screening may help health professional (pharmacists and physicians) to detect clinically significant potential DDIs and avoid unwanted adverse reactions. In future these drug interactions can be effectively controlled by dose adjustments, regular monitoring of blood pressure, renal function, electrolytes, careful use of group of drugs, clinical monitoring of the patient, and laboratory observation of the patient particularly in the cases of major and moderate drug interactions.

References

1. World Health Organization. WHO Drug Information (2005) Geneva: World Health Organization 19: 3-4.
2. Osterhoudt KC and Penning JC. Goodman and Gilman's the Pharmacological Basis of Therapeutics, Brunton LL, Chabner AB and Knollmann CB (Eds) (2011) Drug toxicity and poisoning, McGraw-Hill, New York, USA.
3. Percha B and Altman RB. Informatics confronts drug-drug interactions (2013) Trends Pharmacol Sci 34: 178-184. https://doi.org/10.1016/j.tips.2013.01.006
4. Gupta R. Burden of coronary heart disease in India (2005) Indian Heart J 57: 632-638.
5. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors (2009) PLoS Med 6: e1000058. https://doi.org/10.1371/journal.pmed.1000058
6. GBD Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks 1990-2015: a systematic analysis for the Global Burden of Disease Study (2015) Lancet 388: 1659-1724. https://doi.org/10.1038/sj.bdj.2015.751
7. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries (2016) Circulation 134: 441-450. https://doi.org/10.1161/circulationaha.115.018912
8. US Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors (2013) JAMA 310: 591-608. https://doi.org/10.1001/jama.2013.13805
9. Forouzanfar MH, Liu P, Roth GA, Ng M, Marczak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015 (2017) JAMA 317: 165-182. https://doi.org/10.1001/jama.2016.19043
10. Lewington S, Clarke R, Qizilbash N, Peto R and Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies (2002) Lancet 360: 1903-1913. https://doi.org/10.1016/s0140-6736(02)11911-8

11. Wei YC, George NI, Chang CW and Hicks KA. Assessing sex differences in the risk of cardiovascular disease and mortality per increment in systolic blood pressure: a systematic review and meta-analysis of follow-up studies in the United States (2017) PLoS One 12: 0170218. https://doi.org/10.1371/journal.pone.0170218
12. Gupta R. Trends in hypertension epidemiology in India (2004) J Hum Hypertens 18: 73-78.
13. Sivva D, Mateti UV, Neerati VM, Thiruthopu NS and Martha S. Assessment of drug-drug interactions in hypertensive patients at a superspeciality hospital (2015) Avicenna J Med 5: 29-35. https://doi.org/10.4103/2231-0770.154194
14. Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: A scientific statement from the American Heart Association council for high blood pressure research and the councils on clinical cardiology and epidemiology and prevention (2007) Circulation 115: 2761-2788. https://doi.org/10.1161/circulationaha.107.183885
15. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis (2017) JAMA Cardiol 2: 775-781. https://doi.org/10.1001/jamacardio.2017.1421
16. Agrawal KR and Nagpure S. A study on polypharmacy and drug interactions among elderly hypertensive patients admitted in a tertiary care hospital (2018) International J Health and Allied Sci 7: 222-227.
17. Chelkeba L, Alemseged F and Bedada W. Assessment of potential drug-drug interactions among outpatients receiving cardiovascular medications at Jimma University specialized hospital, South West Ethiopia (2013) Int J Basic Clin Pharmacol 2: 144. https://doi.org/10.5455/2319-2003.ijbcp20130306
18. Nag KA, Umesh M and Churi S. Assessment of potential drug-drug interactions in hospitalized patients in India (2011) Asian J Pharm Clin Res 4: 62-66. https://doi.org/10.4103/picr.PICR_145_16
19. Subramanian A, Adhimoolam M and Kannan S. Study of drug-drug interactions among the hypertensive patients in a tertiary care teaching hospital (2018) Perspectives in Clinical Research 9: 9-14. https://doi.org/10.4103/picr.picr_145_16
20. Sivva D, Mateti UV, Neerati VM, Thiruthopu NS and Martha S. Assessment of drug-drug interactions in hypertensive patients at a superspeciality hospital (2015) Avicenna J Medicine 5: 29-35. https://doi.org/10.4103/2231-0770.154194
21. Dinesh K, Subish P, Pranaya M, Ravi Shankar P, Anil S, et al. Pattern of potential drug-drug interactions in diabetic out-patients in a tertiary care teaching hospital in Nepal (2007) Med J Malaysi 62: 294-298. https://doi.org/10.4321/s1886-36552009000400008
22. Bacic-Vrca V, Marusic S, Erdeljic V, Falamic S, Gojo-Tomic N, et al. The incidence of potential drug-drug interactions in elderly patients with arterial hypertension (2010) Pharm World Sci 32: 815-821. https://doi.org/10.1007/s11096-010-9442-5
23. Radosevic N, Gantumur M and Vlahovic-Palcevski V. Potentially inappropriate prescribing to hospitalised patients (2008) Pharmacoepidemiol Drug Saf 17: 733-737. https://doi.org/10.1002/pds.1531
24. Patel PS, Rana DA, Suthar JV, Malhotra SD and Patel VJ. A study of potential adverse drug-drug interactions among prescribed drugs in medicine outpatient department of a tertiary care teaching hospital (2014) J Basic Clin Pharm 5: 44-48. https://doi.org/10.4103/0976-0105.134983
25. Sivva D, Mateti UV, Neerati VM, Thiruthopu NS and Martha S. Assessment of drug-drug interactions in hypertensive patients at a superspeciality hospital (2015) Avicenna J Med 5: 29-35. https://doi.org/10.4103/2231-0770.154194
26. Chelkeba L, Alemseged F and Bedada W. Assessment of potential drug-drug interactions among outpatients receiving cardiovascular medications at Jimma University specialized hospital, South West Ethiopia (2013) Int J Basic Clin Pharmacol 2: 144. https://doi.org/10.5455/2319-2003.ijbcp20130306
27. Juhlin T, Björkman S and Höglund P. Cyclooxygenase inhibition causes marked impairment of renal function in elderly subjects treated with diuretics and ACE-inhibitors (2005) Eur J Heart Fail 7: 1049-1056. https://doi.org/10.1016/j.ejheart.2004.10.005
28. Kroner BA. Common drug pathways and interactions (2002) Diabetes Spectr 15: 249-255.
29. May M and Schindler C. Clinically and pharmacologically relevant interactions of antidiabetic drugs (2016) Ther Adv Endocrinol Metab 7: 69-83.
30. Kothari N and uly GB. Potential Drug-Drug Interactions among Medications Prescribed to Hypertensive Patients (2014) J Clinical and Diagnostic Res 8: 1-4. https://doi.org/10.7860/jcdr/2014/10032.5091
31. Drug interaction checker, Medscape, New York, USA. http://reference.medscape.com/drug-interactionchecker
32. Michel T and Hoffman BB. Goodman and Gillman's-The Pharmacological Basis of Therapeutics, Brunton LL, Chabner BA and Knollman BC (Eds) (2011) Mc Graw Hill, New York, USA 745-788.
33. Bista D, Saha A, Mishra P, Palaian S and Shankar PR. Pattern of potential drug-drug interactions in the intensive care unit of a teaching hospital in Nepal: a pilot study (2009) J Clinical and Diag Res 3: 1713-1716.
34. Pamu S, Singh T, Ravi S and Ranganayakulu SV. Evaluations of Drug-Drug Interactions in Hypertensive Patients in Secondary Care Hospital (2017) IOSR-JPBS 12: 45-50. https://doi.org/10.9790/3008-1202044550