

DRUG INTERACTION AND ADR AMONG THE ELDERLY HYPERTENSIVE PATIENTS IN A TERTIARY CARE HOSPITAL: A CROSS SECTIONAL STUDY

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Abstract

Objective: This study was conducted to assess the drug interaction and experienced ADRs among the Elderly HTN patients in Tertiary Care Teaching Hospital.

Method: A Quantitative descriptive study of HTN patient's on drug-drug interactions and experienced ADRs among elderly patient was conducted from May 2018 to November 2018. The face-to-face interview adopted in 332 elderly hypertensive patients with random sampling technique SPSS version 20.0 was used for Data analysis.

Result: the result showed that elderly patients experienced ADRs by (ARB and CCB). The majority 37 (11.14%) and 15(4.15%) were experienced ADR by CCD (Edema in lower limbs) and ARB (Muscle weakness, tiredness) respectively. the prevalence of OTC drug use was found to be 32.53 %. Among the co-morbidity the majority of them had dyslipidemia followed by diabetes in single while in double the higher percentage was found in DM + Dyslipidemia (12 %) followed by COPD+DM (3%) and there was equal percentage of multiple comorbidity 1.2%, in COPD+Dyslipidemia+DM and COPD +CKD+DM. The result showed that the potency of drug-drug interaction among the elderly hypertensive patients was found to be 43.37%, among which 79.38%, 6.18% and 14.43 % were moderate, major and minor respectively. Among the other antihypertensive drug aspirin was the most common interacting drug

Conclusion: The drug-drug interaction among the elderly hypertensive patients was common, although there is limited research on elderly patients, where they are vulnerable group, who need more care for the management of drug and disease related problems. They are at high risk of occurrence of drug interactions and ADRs; there fore the awareness and drug proper management by the clinical pharmacist is required for solving the combination drug related issue in older hypertensive population

Keywords: elderly, hypertension, Drug-drug interaction, ADRs

Introduction

Globally hypertension is a major health problem, which annually causes more than 13 % of death [1] In Nepal, the prevalence of HTN increases constantly which has been estimated to range from around 19% to 42% [2]. The elderly population accounts more than 60 % of the world population [3] as the people become older they are at the higher risk of drug toxicity and ADRs, which is due to alteration in pharmacodynamics and pharmacokinetic properties of the elderly people that affect drug absorption, volume of distribution, metabolism and drug clearance leading to toxicity. [4–6]. Besides there is variation in drug response due to alteration in number of receptor and modification of receptor affinity also due to age related decline of homeostatic mechanism [7, 8].

The drug-drug interaction is the effect, which occur by the alteration of one drug to another when it taken concomitantly [9]. The effect of a DDI result in decline of therapeutic effect of drug, which increases the prevalence of ADRs, thus compromised treatment outcomes. [10, 11]. Elderly people are more prone to potential drug interaction, which may be due to multiple prescribers and polypharmacy [12]. DDIs are more likely to occur in the elderly groups, as they use multiple therapies due to multiple comorbidities and have altered pharmacokinetics because they tend to use multiple medications and have altered pharmacokinetics [5, 13].

Adverse drug reactions (ADRs) and drug interactions are the most common cause of frequent hospital admission to the elderly people. In older people are a common cause of

admission to hospital [14, 15], are common in elderly patients in hospital [16], The serious drug interactions included aged ≥ 85 years [17]. Elderly who took five or more drugs had a significantly higher risk of DDI-related ADRs than those who took three to four drugs [18]. A systematic literature review showed that the number drugs as the most frequently documented independent patient-related risk factor for serious ADRs in both the general adult population as well as in the elderly [19]. Despite the fact that the elderly patients are at high risk of having drug interaction and potential adverse outcomes, studies in this regard are scarce in resource-limited settings. The aim of this study was to assess the prevalence and determinants of potential DDIs and reported ADRs in elderly Hypertensive patients.

METHODS

Study Design

This descriptive, cross-sectional study was conducted at the Outpatient Department (OPD) Pharmacy of Chitwan Medical College Teaching Hospital (CMCTH), Bharatpur, Nepal, from May 2018 to November 2018. Ethical approval of this study was obtained from the Chitwan Medical College -Institutional Review Committee (CMC-IRC-2075-03)

Study Population

Elderly (age ≤ 65) hypertensive patients on antihypertensive therapy, who was visited to medicine OPD of Chitwan Medical College and Teaching Hospital were enrolled in the study. A total of 332 patients were administered a structured questionnaire to collect data in the study using a random sampling technique.

Data collection Procedure

Written consent was taken from the patients before enrolling them in the study. All information was collected in a well-designed data collection form, which included socio-demographic: age, sex, and educational status, smoking behavior and clinical characteristics: Experience ADRs, any comorbidities, health experience, health behavior, number and frequency of medicine taken.

Data Analysis

Descriptive statistics were performed using SPSS version 23 and Microsoft excels 2007. Both Inferential test and non-inferential test method was applied. For the presentation of data, several graphical tools like table, charts were used. The variables were presented as the frequency and their respective percentage.

Results

The socio-demographic characteristics of the respondents are shown in Table 1. Out of 332 patients, the majority of 51.20% were females. The majority of the respondents [176 (53%)] were in the age group 65-70 which is followed by [125 (37.7%)] and [31 (9.3%)] in the age group 71-80 and >80 respectively. The majority [315(94.87)] were Hindu and [239(72 %)] of respondents were married most of them were illiterate [298(89.8 %)] and the majority [289 (87.04%)] of respondents were involved in agriculture. The majority [187(56.3 %)] of respondents had positive history of hypertension and only [19(5.7 %)] of respondents were

current smoker.

Table 1: Socio-demographic characteristics of the respondents (n = 332)

n=332	
Variables	Frequency (%)
Age	
65-70	176 (53)
71-80	125 (37.7)
>80	31 (9.3)
Sex	
Male	162 (48.79)
Female	170 (51.20)
Religion	
Hindu	315 (94.87)
Buddhist	12 (3.61)
Muslim	2 (0.32)
Christian	1 (0.30)
Other	2 (0.32)
Marital status	
Married	239 (72)
Divorced	2 (0.6)
Widow/Widower	91 (27.4)
Education	
Illiterate	298 (89.8)
Primary School level/SLC	19 (5.72)
Secondary	7 (2.10)
Post Secondary	6 (1.80)
Bachelor and above	2 (0.6)
Occupation	
Agriculture	289 (87.04)
Government	26 (7.83)
Private	1 (0.30)
Self-employed	14 (4.21)
Unemployed	2 (0.60)
Family history of HTN	
Positive	187 (56.3)
Negative	120 (36.1)
No Record	25 (7.5)
Smoking	
Never	234 (70.5)
Former	79 (23.8)
Current	19 (5.7)

OTC drug use or not in intervention and control group

The prevalence of OTC drug use was found to be 108 (32.53%) where 224 (67.46%) of respondents were not taking OTC drug.

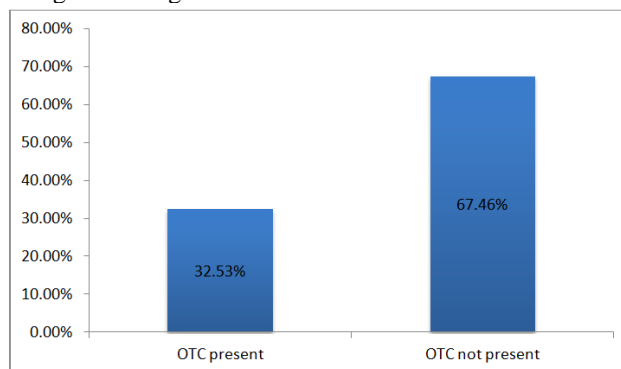


Figure 1: OTC drug use in study group.

The ADRs experienced by the patients

All most all respondents experienced ADRs by (ARB and CCB). The majority 37 (11.14 %) of respondents were experienced ADR (Edema in lower limbs) by CCB where

as 15 (4.51%) of respondents were experienced ADRs by ARB (Muscle weakness, tiredness).

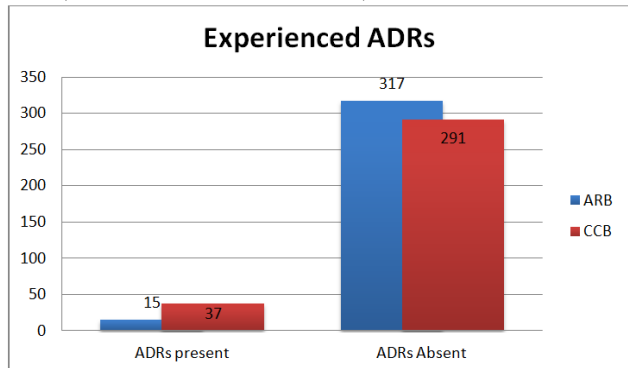


Figure 2: The ADRs experienced by the patients
The comorbidity associated with hypertension in elderly patients

The result showed 57.53% of Comorbidity in elderly hypertensive patients, among which the majority of them had dyslipidemia followed by diabetes and least of them had BPH.

Single Comorbidity

Majority of 26% of respondents had Dyslipidemia followed by Diabetes 22.2% and Thyroid 13.8 % respectively.

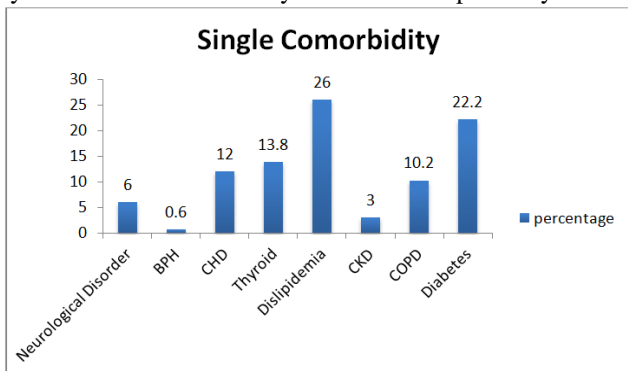


Figure 3: Single Comorbidity associated with Hypertension
Double Comorbidity

Majority of 12% of respondents had DM+Dyslipidemia, followed by 3% of respondents had COPD+DM.

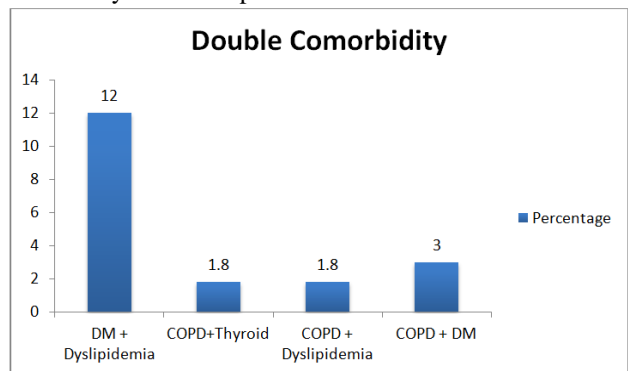


Figure 4: Double Comorbidity associated with Hypertension
Multiple Comorbidity

Majority of 1.2% respondents had COPD+Dyslipidemia+DM in and 1.2% of respondents had

COPD+DM+CKD.

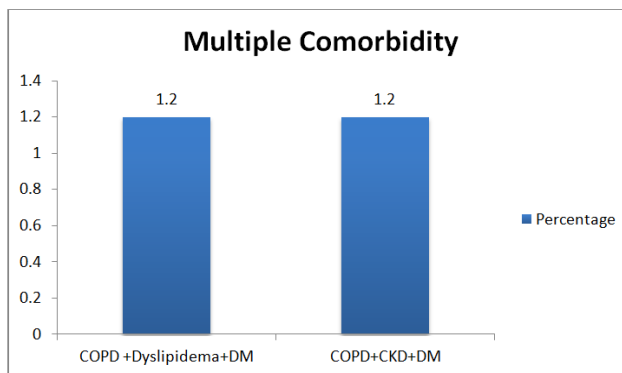


Figure 5: Multiple Comorbidity associated with HTN
Drug interactions

The result showed 43.37% drug interaction, among which 79.38%, 6.18% and 14.43% were moderate, major and minor respectively.

Table 1: Drug-drug interactions

Interaction	Drugs	Number of Interaction
Major	Enalapril+losartan	2
	Methotrexate+pantoprazole	1
	Amiodarone+alfuzosin	1
	Amiodarone+frusemide	1
	Amiodarone+digoxin	1
	Amiodarone+hydrochlorothiazide	1
	Clopidogrel+rabeprazole	4
	Spironolactone+losartan	10
	Clopidogrel+esomeprazole	2
	Atorvastatin+fenofibrate	2
	Amiodarone+frusemide	1
	Enalapril+Spironolactone	1
Moderate	Aspirin+Amlodipine	29
	Metoprolol +Amlodipine	10
	Metoprolol + Hydrochlorothiazide	8
	Atorvastatin +pantoprazole	28
	Insulin lispro+pioglitazone	2
	Losartan +insulin lispro	3
	Aspirin+insulin lispro	1
	Metoprolol+insulin lispro	4
	Enalapril+insulin lispro	2
	Atenolol+insulin lispro	1
Minor	Others	415
	Enalapril+sodium bicarbonate	1
	Metoprolol+levothyroxine	4
	Atenolol+aspirin	9
	Aspirin+spironolactone	8

Table 3: Some Drug-drug interactions observed in elderly Hypertensive Patients

Interaction	Drugs	Comment
Major	Enalapril+losartan	Combination may increase side effects like low blood pressure and increased blood potassium.
	Methotrexate+pantoprazole	pantoprazole oral increases levels of methotrexate sodium oral by reducing drug clearance through the kidneys
	Amiodarone+digoxin	Amiodarone will increase the level or effect of Digoxin by P-glycoprotein (MDR1) efflux transporter.
	Amiodarone+hydrochlorothiazide	Amiodarone will increase the level or effect of hydrochlorothiazide by basic (Cationic) drug competition for renal tubular clearance.
	Sodium bicarbonate + Enalapril	Sodium bicarbonate decreases effect of Enalapril by unspecific interaction mechanism.
	Clopidogrel+rabeprazole	Rabeprazole decreases effect of clopidogrel by affecting hepatic enzyme CYP2C19 metabolism
	Spirolactone+losartan	Both increases serum potassium
	Clopidogrel+esomeprazole	Esomeprazole decreases effect of clopidogrel by affecting hepatic enzyme CYP2C19 metabolism
	Atorvastatin+fenofibrate	Increases effect of other by pharmacodynamics synergism.
Moderate	Aspirin+Amlodipine	Combination may increase the blood pressure
	Metoprolol +Amlodipine	Additive effects in lowering blood pressure and heart rate.
	Metoprolol + Hydrochlorothiazide	Metoprolol increases and hydrochlorothiazide decreases serum potassium.
	Atorvastatin +pantoprazole	Combination may increase the blood levels and effect of atorvastatin.
	Insulin lispro+pioglitazone	Increase the effects of the other by pharmacodynamics synergism.
	Losartan +insulin lispro	Losartan increases effects of insulin lispro by unspecified interaction mechanism
	Metoprolol+insulin lispro	Metoprolol may increase the risk, severity and duration of hypoglycemia in patient receiving insulin lispro.
	Enalapril+insulin lispro	The hypoglycemic effect of insulin may be potentiated by ACE inhibitors.
	Aspirin + Insulin Lispro	May increase the risk of hypoglycemia or low blood sugar
Minor	Atenolol +Aspirin	Both increase serum potassium
	Spirolactone +Aspirin	Both increase serum potassium

Discussion

In this present study the prevalence of OTC drug use was to be 108 (32.53%). Older adults generally have more medical problems and use more medications, both prescription and OTC, when compared to younger adults. Many older adult

patients self-treat using OTC medications. Older adults account for about 13% of the United States population and purchase 40% of all OTCs consumed (Berardi et al., 2006). Pharmacists, as one of the most accessible health care providers, have an opportunity to assist these patients when making decisions in the OTC aisle. As the baby boomers age, there will be even more opportunities for pharmacists to assist older adults with making appropriate OTC medication choices. To do this successfully, it is essential for pharmacists to be able to evaluate and assess patient symptoms.

The change in drug therapy by the doctor due to the suspected ADRs experienced by the patients was recorded. According to which, the Experienced ADR by the patients with ARB (Amlodipine) were found to be 15 (4.51%), while the Experienced ADR with CCB (Losartan Potassium) was found to be 37 (11.14%). The most commonly experienced ADR were muscle weakness, tiredness and Edema of lower limbs, which was, might be due to Losartan and Amlodipine respectively. The Garrett et al., 2003 showed that the frequency of ADRs was 6% when a patient takes 2 drugs, 50% when a patient takes 5 drugs, and almost 100% when a patient takes 8 or more drugs and another cohort study done by Ahmed et al., 2014 showed the occurrence of ADRs was 10.5% among the patients. The reasons for increased adverse drug events associated with older adults are multifactorial. Older adults are more likely to be frail, have a higher likelihood of multiple comorbidities, and are more likely to incur errors with self-administration of their medications, resulting in increased non-adherence with polypharmacy.

This present study showed that 57.53% of the patients have comorbidity among them dyslipidemia and diabetes were the commonest in single comorbidity associated with HTN and among double and triple comorbidity DM+Dyslipidemia followed by COPD+DM and COPD+Dyslipidemia+DM followed by COPD+DM+CKD respectively. The association between the comorbidity and non-adherence score was not performed in this present study. The Co-morbidities can worsen patient's conditions and make them less likely to adhere to their antihypertensive drugs. Patients with chronic co-morbidities requiring additional medications could suffer from complex treatment regimens, which may mitigate adherence to medications in addition to the possibility of an associated depressive illness, study done by Amanda et al showed that up to 75% of adult with diabetes also have HTN and patient with HTN alone often show evidence of insulin resistance. Otsuka et al showed that dyslipidemia is significantly associated with an increased risk of developing hypertension in an Asian population. The reason behind these multiple Comorbidities showed that the elderly hypertensive patients might have risk for multiple disease and due to this polypharmacy is exist, that could be the possible reason for non adherence to those patients.

Drug-drug interactions can increase the frequency and severity of adverse events (AEs) or increase the likelihood of treatment failure. DDI assessment is therefore, a critical

component and regulatory evaluation. Empirical evidence of decreased efficacy or increased severity or frequency of AEs is the most clinically relevant measure of a DDI (Rekic et al., 2017). In this study mainly DDI can be categorized into three conditions in HTN i.e. minor, moderate and major. The minor DDI leads to the condition like dizziness, weakness, headache, and constipation. Similarly the moderate DDI causes blood clots, shortness of breathe, chest pain, sudden loss of vision, redness and swelling in an extremity, etc. Likewise major DDI leads to hyperkalemia, kidney failure, muscle paralysis, cardiac arrest, and heart failure.

This present study showed that 43.37% of patients were exposed to DDI this result is consistent with another study done by Subramanian A et al., 2018, which showed that the 48% of patients were exposed to at least one DDI and 71.50%, India by Kothari N 2014. According to Kothari N, the Drug-drug interaction between atenolol & amlodipine was the most common DDI (136) followed by metoprolol and amlodine (88).

The current study showed, there was 58.43% DDIs, among which, 6.18%, 79.38%, 14.43% were major, moderate, and minor DDI respectively, Agrawal RH and Nagpure S, 2018 reported that the most common drug interaction was moderate (50.62%) followed by mild (8.64%) and severe (7.94%). when compared to a study conducted by Bjorkman et al. in 2002, in which there were drug interactions in 46% of patients. Furthermore, a study conducted by Gosney M showed potential drug-drug interactions in 33% of all prescriptions in admitted elderly patients.

The most common DDI in major category was Spironolactone+Losartan, followed by Clopidogrel+Rabeprazole and in the Moderate the common DDI was Aspirin+Losartan. study done by Subramanian et al 2020, revealed that the Spironolactone/enalapril, spironolactone/ telmisartan, and spironolactone/carvedilol. Also had caused potential DDIs, and these combinations also increase serum potassium levels.

The present study showed that among the antihypertensive interacting with other cardiovascular agent, aspirin was most commonly involved in DDI, the interactions were Aspirin+ Spironolactone, Aspirin + Atenol, Aspirin+Amlodopine and Aspirin + Insulin Lispro, this result was supported by another study Subramanian et al 2020, according to which Aspirin/enalapril, aspirin/atenolol, aspirin/ furosemide, aspirin/spironolactone, aspirin/carvedilol, and aspirin/metoprolol were the common interactions reported. The study showed that the ACE inhibitors and insulin lispro result the potential DDI, where the study done by May M and Schindler, 2016 revealed the use of ACE inhibitors with Sulfonylureas increase the insulin sensitivity and potentiate the risk of Hypoglycemia, The reason behind the high percentage of drug-drug interactions might be due to inappropriate therapy and lack of patients counseling.

Conclusion

The finding of present study reveals that nearly fifty

percentages of the elderly hypertensive patients are exposed to at least one potential DDIs. Around fifty percentages of Elderly patients have probable chance of having comorbidities and 32.53 % prevalence of using OTC drug. This study showed that the ADRs experienced by elderly patient is mainly due to CCB and ARB among the hypertensive patents. Thus Identifying and preventing potentially harmful DDIs is a critical component of a Clinical pharmacist's mission and the potential DDIs and making appropriate dosage or therapy adjustments.

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