Assessment of adverse drug reactions profile of anti-hypertensive agents in Tertiary Care Hospitals, Bhopal.

[*1]Sonali Meshram [2]Dr. Rahul Raghunath Bhalsinge

[*1]Ph.D. scholar, Department of Pharmacology, L.N. Medical College and J.K. Hospital, LNCT University, Bhopal
[2]Professor, Department of Pharmacology, L.N. Medical College and J.K. Hospital, LNCT University, Bhopal

Author of Corresponding:*Sonali Meshram

Sonalimeshram110786@gmail.com

Abstract:

Background:

Adverse drug reactions (ADR) are the immediate or delayed effects of drugs generally caused by drugs. Pharmacovigilance have played a vital role in the reporting of short-term as well as long-term information about adverse drug reactions. The present study focused to monitor ADRs of anti-hypertensive agents and assessment of adverse drug reactions in hypertensive patients on the basis of age, gender, system-wise distribution, and drug utilisation pattern.

Methods: Total 150 patients were evaluated for the adverse effects of anti-hypertensive agents in tertiary care hospitals in the Bhopal region. ADR has been reported on the basis of medical history, history of drugs, and severity of the adverse drug reaction. Causality assessment was done using the Naranjo scale.

Results: Total 30 patients (20%) with a mean age of 63.27 ± 3.21 years complained of adverse effects. Out of 30 patients, 17 (56.67%) were females and 13 (43.33%) were males. The age group involved in reporting ADRs was more than 50. Statistically significant differences ($p < 0.05$) obtained on adverse drug reactions reported by different age groups. The most common reported adverse effects were dry cough, vertigo, headache, palpitation, edema, gastric discomfort, and rashes. The most common prescribed agents were CCBs, ACEIs, ARBs, beta-blockers, and diuretics. On the probability scale of adverse drug reactions, 03 were certain, 05 probable, 07 possible, 03 conditional, 04 unlikely, and 08 un-accessible.

Conclusion: Keen observation of hypertensive agent enhance alertness and awareness about reporting of adverse drug reactions among health care providers.

Key words: adverse drug reaction; Anti-hypertensive agent; Naranjo scale

Introduction:

Adverse drug reactions created biggest disaster in the world on 1950 as thalidomide tragedy, this incident raised the concern in health care professional to pay attention over adverse drug reactions reporting. After this event the reporting of adverse drug reactions has been increased, it is necessary to know the short term and long-term effects of drug for effectively management of disease in animals & humans is necessary. Our study has also provided evidence on adverse drug reactions of anti-hypertensive agents this study was entitled as assessment of adverse drug reactions profile in hypertensive patients at tertiary care hospitals in Bhopal. On 1963 WHO implemented program for international drug monitoring, in 1978 in collaborating centre for international drug monitoring was established in Uppsala monitoring centre India has started pharmacovigilance activities since 1983 increases news after Thalidomide event changed the dynamics of health care management this event represented with 10,000 children's developed seal like limb deformity due to its teratogenic effect. ADRs one of the leading causes of death

in world. It ranked 4th to 6th leading cause of death in U.S. Adverse drug reactions occurred dosage normally used in humans, The management of non- communicable disease have reported ADRs in literature we have found in this study adverse drug reactions of anti-hypertensive agents, Hypertension is one of the risk factors for cardiovascular morbidity & mortality. Incidence of hypertension increases the risk of coronary artery disease, heart failure, angina and stroke. Effective therapies decrease the chances of cardiovascular co-morbidities. The benefit of drugs always related with the harmful effects of them. The treatment of hypertension based on life style modification and pharmacotherapy. In 2010, 1.39 billion people had hypertension, in 2016 the prevalence of is 29.8% in India[2]. This prevalence is rising globally to ageing of the population and increases in exposure to lifestyle risk factor like obesity, lack of physical activity, smoking, high sodium diet, low potassium diet. For reduction drug related reactions continuous reporting of adverse drug reactions is required and it is essential to procure fruitful drugs with lesser side effects. Pharmacovigilance has an aim of safe use of medicines, it is a science helps in reporting of rare ADRs, currently Pharmacovigilance program of India have 672 ADR monitoring centres. It provides us evidence-based directions for application of a drug. WHO has given definition of Pharmacovigilance "It is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems".[6]

It also helps CDSCO and gives guidance for formulating safety related regulatory decisions for medicines. The understanding of adverse drug reactions is necessary for depletion of health problems for achieving good quality of life of a person.[9] ADRs classified into Type A and Type B, in Type A these are dose dependent, based on pharmacological profile of a drug, Type B Bizarre it occurs due to immunological reaction between drug and patient's body these are neither dose dependent nor pharmacological response of drug. Severity of ADR depends upon drug, disease, age and combine use of drugs. Serious adverse drug reactions are responsible for development of drug related event, FDA defines adverse drug event "a serious adverse event as one in which the patient outcome is death, life threatening, hospitalization disability, congenital anomaly or required intervention to prevent permanent impairment or damage".[6]

So, for this we attempted a small study on 150 hypertensive patients by reporting of adverse drug reactions through participants. This study conducted in medicine OPD of J.K. Hospital and other tertiary care hospitals in Bhopal. Five major classes of anti-hypertensive agents prescribed to hypertensive patients such as thiazide diuretics, Calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, Beta blockers have been used.[10] We reported ADRs on the basis of age, sex, system wise distribution and drug utilization pattern.

Methodology:

The ADR reporting has been done by with the help of suspected adverse drug reaction reporting form recommended by central drugs standard control organization, Govt of India.[13]. The pharmacologically treated hypertensive patients who attended routine follow-up at medicine outpatient department in J.K. and other tertiary care hospitals in Bhopal.[11] The study was approved by human animal ethical committee of L. N. Medical college and research centre *(LNCTU/PhD/2019/RDC/PR/001/52)* (approved on 30/08/2019).[12]After getting approval from research committee, After giving informed consent to patients we have asked the patients for reactions and collected ADRs on ADR reporting form. The information collected on the basis of patient's information (Initial, age, sex, height, weight, onset date/ stop date, dose, frequency, route of administration, medical history (past/present), concomitant medication). All patients who were on antihypertensive agents irrespective of age and sex included in this study. Patients taking intensive care, unconscious, mentally retarded were excluded from the study. All the data were kept confidential.[14] The estimation of probability that a drug caused on adverse drug

reaction is usually based on clinical judgement. Events described by hypertensive patients were collected on the basis of drugs, dosage and duration of disease.[15] Causality assessment was done by Naranjo scale. Which divides the causality relationship into certain, probable, possible or unlikely was used for the assessment of nature of ADRs. Statistical analysis was done by Chi-square and analysis of variance test followed by multiple comparisons by Bonferroni Correlation ($P < 0.05$).[16]

Results:

Age wise distribution of ADRs: The mean age of ADR reporting was 63.27 ± 3.21, Most commonly exposed patients were belonging to the age group of 60-70 yrs, ($P<0.001$) and more than 70 years, ($P<0.05$), 14 patients reported ADR by age group between 60-69 yrs., 05 ADR reported by age group between 50-59 yrs age group, 02 ADR reported by age group includes 40-49yr. The difference of ADR reporting on different age group were statistically significant. The age group represents less than 40 yrs. were excluded from this study.[17] ***Table-1***

Gender wise distribution of ADRs: During the study period a total of 150 patients visited L.N. Medical College & J.K. Hospital, tertiary care hospitals in Bhopal. Among 150 hypertensive patients 30 ADRs were reported. On reporting 13 (45.30%) ADRs were reported by male patients and 17 (54.60%) were reported by female patients.[16] ***Figure -1***

System wise distribution of ADRs: Among 150 patients, the significant ADR distribution on different systems, 07 ADRs found from CNS (23.33%), 06 from CVS (20%), 05 (16.66%) ADR involved eye, 04 (13.33%) effected respiratory system 04 (13.33%) and represented musculoskeletal system 08 (26.66%).[18] ***Table-3***

Probability grading: Causality assessment performed by Naranjo scale, we found 03 ADR (9.99%) certain, 05 probable (16.65%), 07 possible (23.32%), 03 (9.99%) conditional, 04 (13.32%) unlikely and 08 (26.65%) were unacessible.[20,21] ***(Figure-4)***

Drug utilization pattern: Most commonly prescribed drug was Amlodipine 34%, Metoprolol 11%, Enalapril 9%, Atenolol, Telmisartan and Nifedipine 9%, 7%, 10%, Ramipril and Thiazide were 5% &15%.[19] ***(Figure-5)***

Table-1: Age wise distribution of ADRs

Age Group	Number of ADR
40-49	6.5+2.12
50-59	7.7+4.04
60-69	10.3+3.99***
70-80	8.4+3.58**

*ADR: Adverse drug reactions; ** significant difference; *** high significant difference*

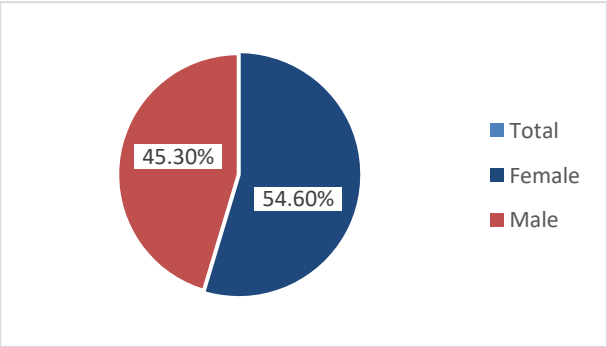

Figure-1: Gender wise distribution of ADR

Table-2: Number of ADR reported by individual drug

Anti-hypertensive Agents	ADRs	No. of ADRs
Amlodipine	Drycough,vertigo,ankle edema, Hypotension	4
Nifedipine	Palpitation,ankle edema,numbness, bloating,	4
Metoprolol	Vertigo,fatigue, vertigo	3
Atenolol	Bradycardia,dizziness,fatigue	3
Enalpril	Swelling in ankles and hands, dry cough	3
Ramipril	Headache, dizziness	2
Telmisartan	Rash,swelling in ankles	2
Diuretics	Frequent micturation,muscle crampls,tingling	9

Table 03: System wise distribution of ADR

Organ System	No. of ADRs	% of ADRs
CNS	07	23.33
Musculoskeletal system	04	13.33
Respiratory System	08	26.66
Eye	04	13.33
CVS	07	23.33
Total	30	100

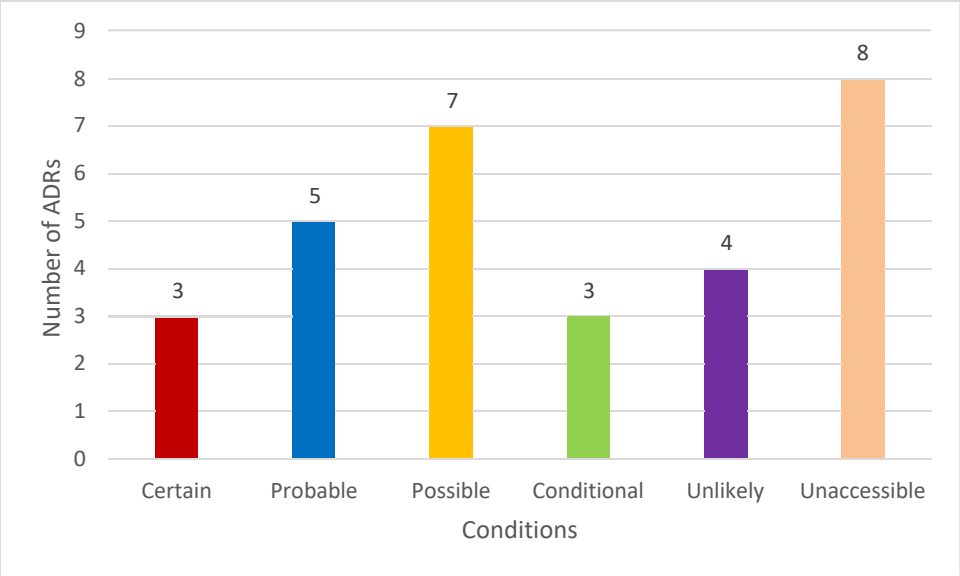

Figure-4: Causality assessment by Naranjo scale

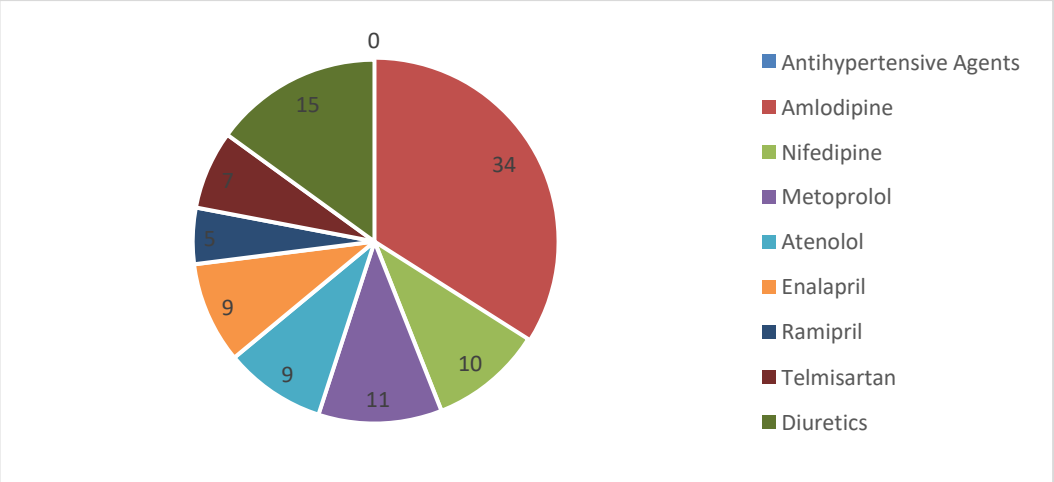

Figure-: Drug utilization pattern

Discussion:

The hypertensive patients reported ADRs on the basis of their experience on drug dose and duration of disease among 150 patients 30 patients reported ADRs. Lavan & Gallgahhar [22] on 2016 said on their study aging is responsible for production of ADRs, in our study reporting significantly done by 60-70 ($p<0.001$) & more then 70 ($p<0.05$). Along with aging gender was also considered an important factor for reporting of ADRs we found in our study females predominance in comparison to males this findings also concluded by Stern on 2008 one female patients on multiple antihypertensive medicines reported Diarrhoea after taking the medicines.[23] Combination therapies has multisystem distribution of ADRs it has been shown by earlier literature In 2011 Elliot studied the effect of CCBs on hypertension, she has shown the high dose of CCBs, β-blockers & Diuretics were involved in ADR production. We have reported ADRs from following system CNS 07 (23.33%), CVS 06 (20%), Respiratory 08 (26.66%), eye 04 (13.33%) and musculoskeletal system 04 (13.33%).[24] Khurshid et al., 2012 found 21 ADR from anti-hypertensive agents, on our study preferred agents were Amlodipine 34%, Metoprolol 11%, Enalapril 9%, Atenolol, Telmisartan and Nifedipine 9%, 7%, 10%,

Ramipril and Thiazide were 5% &15%. Among 30 patients we have found that 9 ADRs from diuretics, 4 from amlodipine, 4 from Nifedipine, 3 Metoprolol, 3 Atenolol, 3 Enalapril, 2 Ramipril & 2 Telmisartan.[25] Probability grading performed by Naranjo scale this assessment earlier used by Seger et al., 2013 he assessed the misuse of Naranjo scale on toxicology on this study 03 ADR (9.99%) certain, 05 probable (16.65%), 07 possible (23.32%), 03 (9.99%) conditional, 04 (13.32%) unlikely and 08 (26.65%) were un-acessible.[26]

Conclusion:

Proper monitoring of ADR reporting is crucial for safe disease management, preventing complications, and improving quality of life. We want to create awareness for ADR reporting through this small prospective observational survey study on the pharmacovigilance of Anti-hypertensive agents.

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