

To Identify Suspected ADRs and Establish Their Causal Relationship with Suspected Drug: An Institutional Based Study

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Abstract

Background: ADRs as any response to a drug that is noxious, unintended and that occurs at a dose used in humans for prophylaxis, diagnosis or therapy, excluding failure to accomplish the intended purpose. The present study was conducted to identify suspected ADRs and establish their causal relationship with suspected drug. **Materials and Methods:** This prospective and observational study was conducted at hospitals in tertiary care teaching hospitals in western U.P. during a period from February 2018 to March 2019. All the necessary and relevant data was collected from patients like case notes, treatment charts, laboratory reports, ADRs notification forms as per CDSCO, patients interview and reporter's interview. The noted ADRs were assessed by using Naranjo's causality of ADR assessment scale. All reported ADRs were evaluated for the following parameters using appropriate scale: Causality (Naranjo's scale), Severity (Hartwig et al scale). Statistical analyses were performed. **Results:** The results showed that females were more reported patients than males who were on antihypertensive medication and over 95% patients were urban. Of all 28% patients were with comorbidities with hypertension. As per the report ADRs were found more among the patient treated with monotherapy of antihypertensives and less among those with polytherapy or fixed drug combination. CCBs have been the most common drug causing some adverse effect leading to discontinuation of drugs. And the most common affected organ system was central nervous system. And drug combination with lesser ADRs is CCB with diuretics which makes them better at treatment with lesser ADRs. The causality assessment done as per Naranjo's scale and WHO-UMC scale which concluded the majority that is more than half of patients were classified as probable under both scales and rest under possible and very few under unlikely. The severity assessment was done as per Hartwig scale and all the patients fell into category of Mild level 1 and 2 which very well parallels with finding of causality scale. **Conclusion:** In the above pharmacovigilance study it was found out that adverse drug reactions reported by the commonly used antihypertensives was least with the poly therapy as compared to monotherapy. Causality assessment was done using Naranjo's probability scale and more than half of reported ADRs were classified as possible and on WHO-UMC more than half of them were probable. Hartwig severity assessment concluded all the ADRs were only, mild and more than 2/3rd were level 2 mild ADRs. AS found the polytherapy with antihypertensives was associated with minimum adverse effects and hence could be preferred over monotherapy considering all the other physical and medical status of patient under control.

Keywords: Hypertension, Antihypertensives, Polytherapy.

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Introduction

Hypertension is a chronic disease and one of the major public health problem and a significant cardiovascular risk factor, where the systolic blood pressure is more than 140 mm Hg and the diastolic blood pressure is more than 90 mmHg[1]. Also hypertension can be explained as an imbalanced hemodynamic function that causes an abnormal and persistent elevation of systemic blood pressure, either systolic, diastolic or both above level of 140/90 mmHg is known as Hypertension. It is also regarded as a silent killer[2]. Worldwide prevalence estimates for hypertension may be as much as one billion individuals, and approximately 7.1 million deaths per year may be attributed to hypertension[3]. About 35% of hypertensive patients discontinue their medication within six months and in at least 50% of cases, the reason for discontinuation relates to adverse effects and patient dissatisfaction[1].

Adverse drug reaction (ADRs) is defined as per WHO 1972, "A response which is noxious and unintended and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function"[4]. Other terms that may be included are:- Side effects, Secondary pharmacological effects, Idiosyncratic reactions, Toxic reactions, Allergic reactions, Hypersensitivity reactions. ADRs as any response to a drug that is noxious, unintended and that occurs at a doses used in humans for prophylaxis, diagnosis or therapy, excluding failure to accomplish the intended purpose[5]. Causality assesment is an intergral component of the medical review process and determines the possibility of an association between the intake of a drug and the occurrence of the adverse event in an individual patient. Causality is crucial for risk benefit assessment, particularly when it involves post marketing safety signals[6]. The present study was conducted to identify suspected ADRs and establish their causal relationship with suspected drug.

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Materials and methods

This prospective and observational study was conducted at hospitals in tertiary care teaching hospitals in western U.P. during a period from February 2018 to March 2019. Patients with any ADRs with well-established causal relationship with different classes of antihypertensive drugs were included in the study. Patient with age group <20yr & >80yr, Pregnancy induced hypertension, Patient with

not well-established causal relationship, patients with allergic reactions due to dust, pollen and insects, patients who rechallenged test for drugs were not included in the study. All the necessary and relevant data was collected from patients like case notes, treatment charts, laboratory reports, ADRs notification forms as per CDSCO (Govt. of INDIA's Performa), patients interview and reporter's interview. ADRs alert forms were self-confirmed framed and implemented in each and every ward of the teaching hospital of Santosh Medical College. The prescriber helped in notify in ADR alert form if they found any ADR in their routine ward rounds. Nurses were also encouraged to note the ADR if any. The noted ADRs were assessed by using Naranjo's causality of ADR assessment scale. The noted ADRs will be grouped into

- Certain
- Probable,
- Possible
- Unlikely
- Unclassified
- Unclassifiable

The patients were classified or categorized according to their

- Demographics,
- Diseases status
- Departments (optional)

The collected ADRs data was reported to the AMC in The Santosh Medical College, Department of Pharmacology and thereafter to IPC. Written informed consent as per prescribed performa and all necessary legal formalities was completed accordingly. The ADRs was recorded in the specified format designed by the CDSCO (Central Drug Standard Control Organisation) for this purpose. Laboratory investigation was done in appropriate cases. Patients were intensively monitored in order to identify suspected ADRs during hospitalization. The types of reactions were classified, and a causal relationship was established using WHO causality scale. In the proposed study the reports of ADRs were evaluated. Further the individual ADR reports were assessed to find out whether the ADR was the reason for the present admission of the patient to the hospital. All reported ADRs were evaluated for the following parameters using appropriate scale

1-Causality (Naranjo's scale)⁷

2-Severity (Hartwig et al scale)⁸

The methods used to detect ADRs were also used to note variation in the reported ADR prevalence rates. Patient's data collection using a specific data collection sheet was used (CDSCO designed for this investigation). Information on drugs, which were used immediately before development of ADR and the symptoms present at the time of patient's admission were collected in an attempt to identify suspected

adverse reactions that started prior to hospitalization. In order to identify and monitor the ADRs during treatment, the medical prescriptions and intercurrents were recorded. The information were transferred to the data collection sheet of CDSCO and on line into VIGIFLOW the final reports print out are maintained as record. Statistical analyses were performed, and the results were interpreted according to WHO probability assessment scale and Naranjo's causality assessment scale.

Results

The study was conducted in tertiary teaching hospitals in western U.P. The present proposed study included 200 patients (18-70 yr) reported suffering from hypertension: visiting different departments of hospital from Feb 2018 to March 2019. It's evident that the % of hypertensive patients were maximum in age group of 31 to 64 age group (88%). It shows the number of female patients is more than male patients which is 45 and 55% resp. Demographically patients divided into urban 94% and rural 6%.

Table 1 describes the no of patients with and without comorbidities i.e. 28% and 72% respectively.

Table 2 describes the comorbidities that were found coexisting among the reported cases of ADR due to antihypertensives which was a total of 28% of all.

Table 3 shows the 70% of ADRs reported were due to single drug users and fixed dose combinations showed 13 % ADRs. Polypharmacy (included single and multiple drugs) was 16%.

Table 4 shows the antihypertensive classes used for treatment. Of which calcium channel blockers were the drugs with the maximum reported ADRs (39%) followed by ARBs (37%), Diuretics (15%) and ACEI, beta blocker and alpha blockers as 4%, 3% and 2% resp.

Table 5 showed the maximum reported fixed dose combination of antihypertensives was of ARB +CCB was 50 % followed by ARB + Diuretic 45%, CCB + Diuretic 10%, ARB+BB 5% and CCB+BB 2%.

Table 6 details organ system wise adverse reaction that were reported which included the maximum of 63% of central nervous system and 35% of cardiovascular followed by 27% of musculoskeletal, 11% of gastrointestinal and a least of 2% and 1% of ophthalmic and ENT ADRS resp.

Table 7 Causality assessment as per WHO-UMC classified 62% as likely, 29% as possible and 9% as unlikely.

Table 8 Naranjo's scale concludes that more than half of reported ADRs are classified 71% as probable and 29% as possible.

Table 9 shows on Hartwig severity scale only Level 1 and 2 were the categorization reported antihypertensives were falling under and Mild level 1 and 2 constituted 19 and 81% respectively.

Table 1: Comorbidities associated among ADR reported patients.

Comorbidity	Total	%
Present	56	28
Absent	144	72

Table 2: Comorbidities carried among the reported patients

Comorbidities	Total	%
CAD	4	7.14
DM II	14	25
Hyperlipidemia	8	14.28
Thyroid disorder	12	21.43
COPD	12	21.43
BPH	6	10.72
TOTAL	56	

Table 3: ADRs reported as Monotherapy, Fixed drug combination, polypharmacy.

Therapy	Total	%	ADRs	%
Monotherapy	114	52.7	492	70.4
Fixed drug combination	46	21	94	13.3
Polypharmacy	56	27	112	16
TOTAL	216		698	

Table 4: Individual drug classes and reported ADRs

Drug Class	Total of drugs	%	ADRs reported	%
Calcium Channel Blocker	58	41	191	39
ARBs	42	29.5	180	36.5
Diuretics	22	15.4	75	15.2
ACEI	8	5.6	20	4
Beta Blockers	6	4.2	18	3.6
Alpha Blocker	6	4.2	8	1.6
TOTAL	142		492	

Table 5: Number of Drug combinations in dual therapy/fixed drug combination that reported ADRs.

Drug combination	Total	%	ADRs	%
ARB+CCB	20	43.48	42	50
ARB+DIURETIC	16	34.78	38	45.24
CCB+DIURETIC	6	13.04	8	9.52
ARB+B BLOCKER	2	4.35	4	4.76
CCB+B BLOCKER	2	4.35	2	2.38
TOTAL	46		84	

Table 6: List of Adverse drug reaction organ system wise

Organ system	Total	%
Central nervous	140	63.64
Cardiovascular	76	34.55
Musculoskeletal	60	27.27
Gastrointestinal	24	10.91
Ophthalmic	4	1.82
ENT	2	0.91
TOTAL	220	

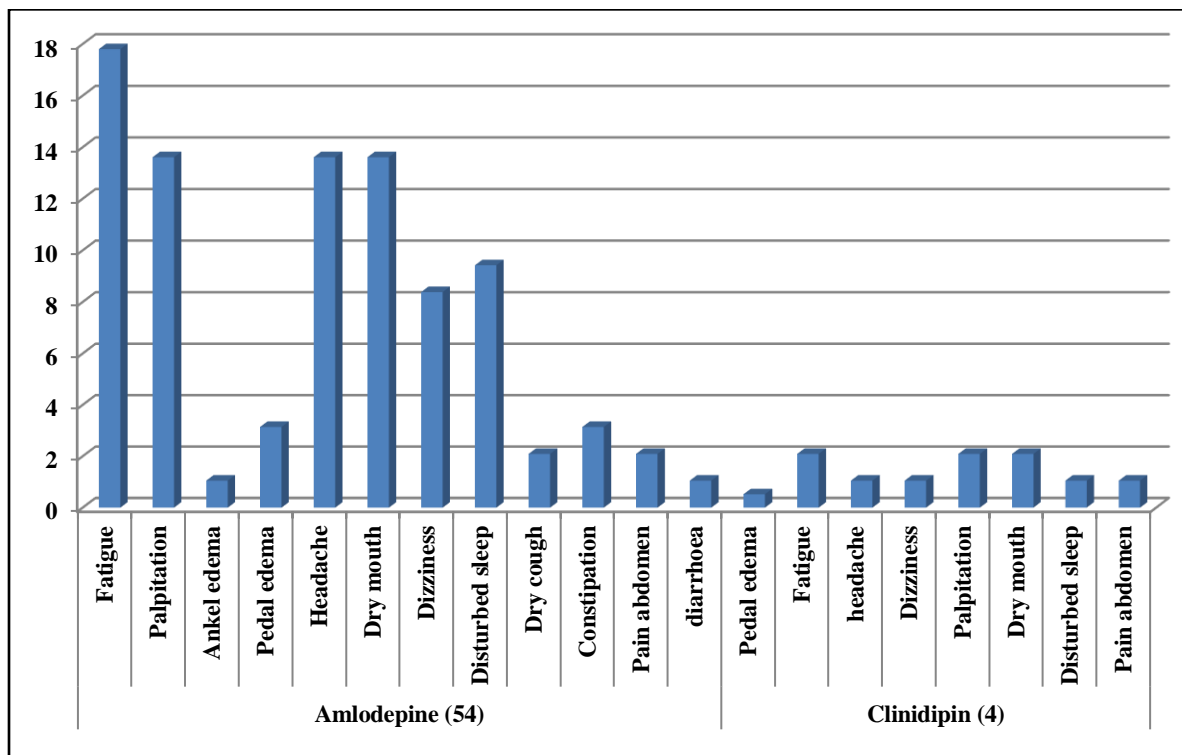
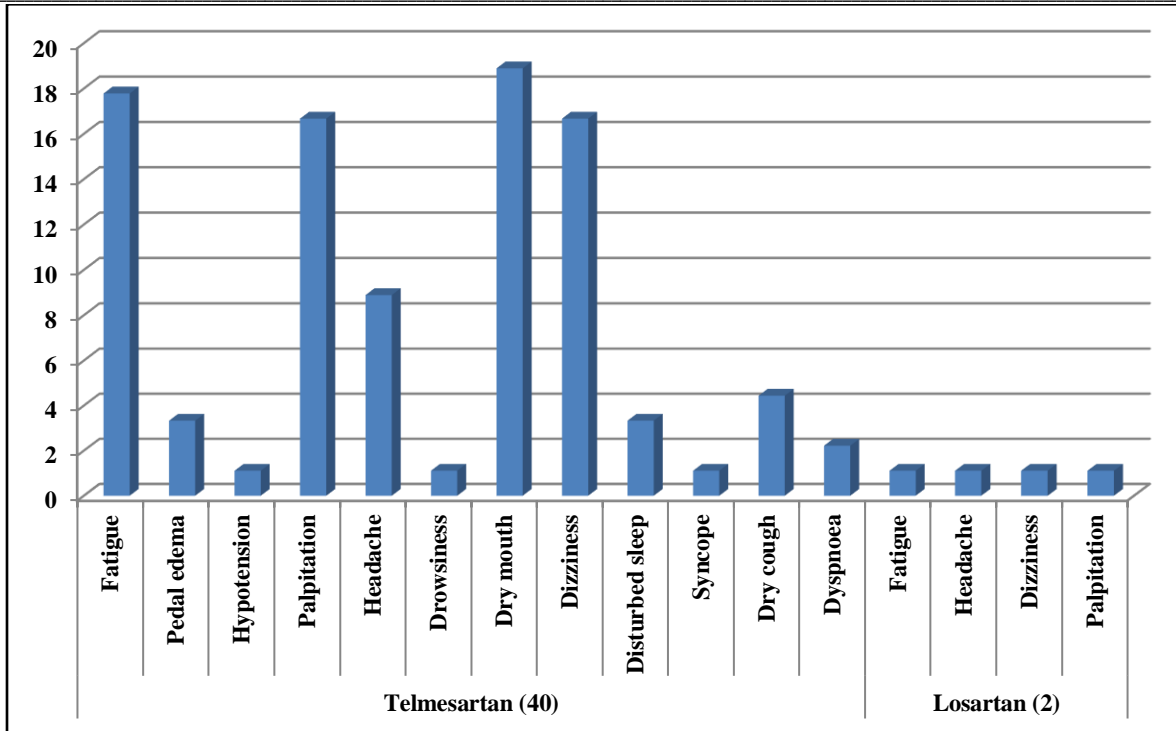
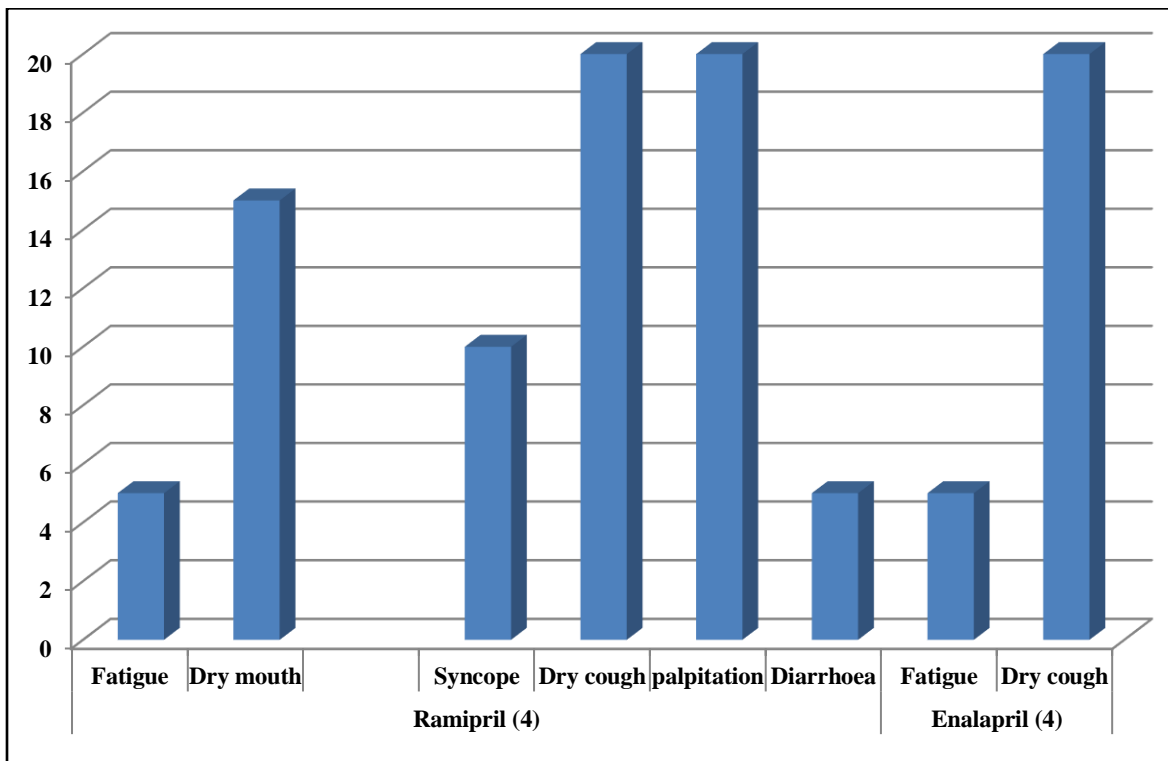


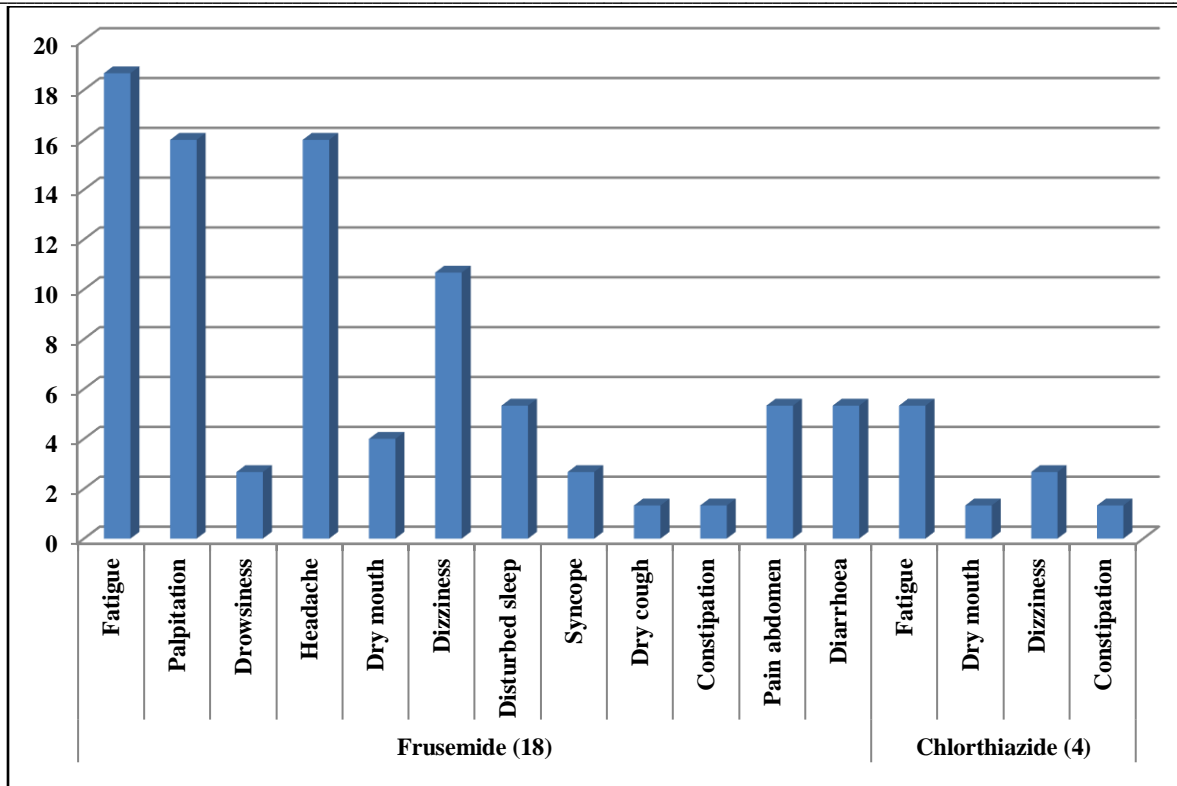
Table 1: Drugs related observed Adverse Drug Reactions
a. Calcium Channel Blocker



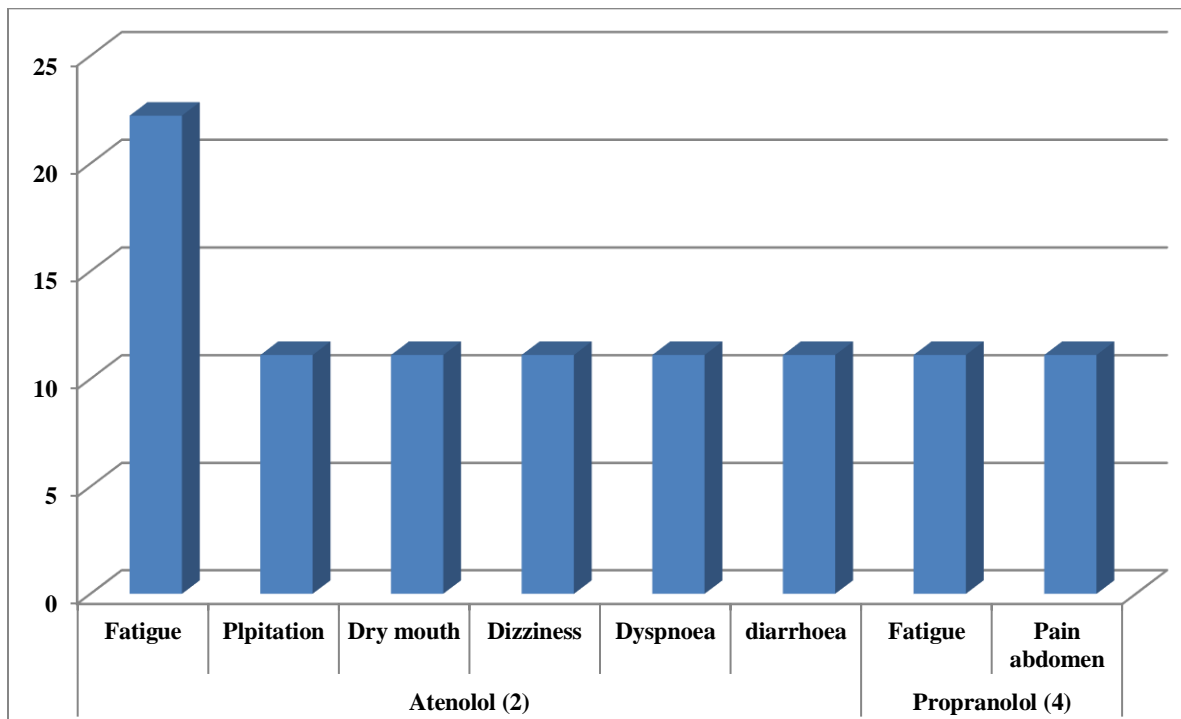
b. Angiotensin Receptor Blocker



c. Angiotensin Converting Enzyme Inhibitor

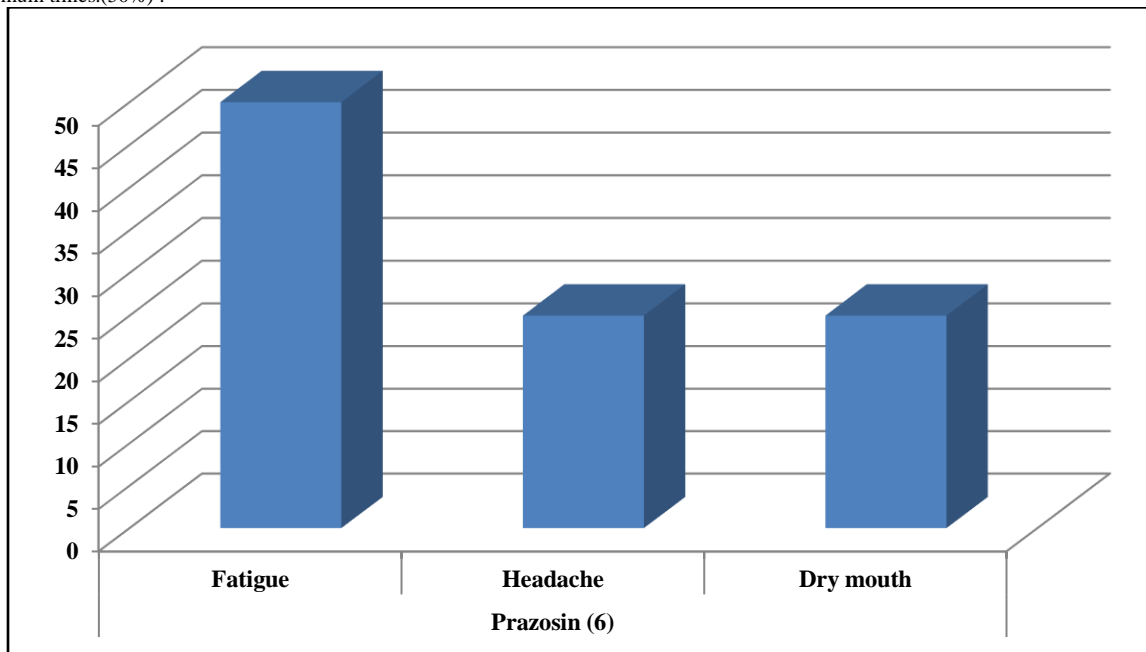


d. Diuretics



e. Beta Blocker

Table 10(f) details individual reactions reported by the alpha receptor antagonist where fatigue was the adverse reaction occurring for the maximum times.(50%) .



f. Alpha receptor antagonist

Table 7: Causality assessment as per WHO-UMC guidelines

ADRs	Total	%
Certain	-	-
Probable/Likely	124	62
Possible	58	29
Unlikely	18	9

Table 8: Causality assessment as per Naranjo’s scale

	Total	%
Definite	-	-
Probable	142	71
Possible	58	29
Doubtful	-	-

Table 9: Severity assessment as per hartwig scale.

LEVEL	TOTAL	%
Mild (Level1)	38	19
Mild (Level2)	162	81

Discussion

The result from this study shows that the prevalence of hypertension is highest in age group 31 to 64 years. Okoduwa’s (2013) study indicated that prevalence of hypertension is highest in age group 60-69 and 50-59[9].

A follow up program by J. David Curb et al which parallels with our finding that occurrence of ADRS lead to discontinuation of treatment[10].

Ghafoorunisa, 1985[11] supports our observation that the incidence and associations of CHD are seen more in advanced age group.

The demographic details of our study population showed female gender predominance over male, which was similar to that reported in study of Ramesh M et al[1].

Our study contained majority of urban population reporting ADRs than rural.

Contrarily Goyal et al. reported changes in risk factors in a rural Punjab population over a 20-year period from 1994 to 2012 and reported increase in hypertension prevalence from 15% to 27%[13].

Contrary to my study where ADR by monotherapy patients were more the percentage of polytherapy was highest in hypertensive patients in similar Arshad HM[14].

Supporting my study that combination therapy seems to be a more rational approach to reduce cardiovascular risk factor in hypertension was found similarly in study by Manicia G et al[15].

In a large meta-analysis, including 48,220 patients, Psaty et al. found that high-dose diuretic therapy reduced the risk of stroke much more than therapy with β -blockers proving it to be more preferred and beneficial drug with less ADRs[16].

Klungel et al[17]. in their study showed that among 1,237 single-drug users with no history of cardiovascular disease, the adjusted risk of ischemic stroke was 2 to 2 1/2 times higher among users of β -blockers, calcium antagonists, or ACE inhibitors than among users of a diuretic alone. Interestingly, even in patients with cardiovascular disease, diuretics still conferred a lower stroke risk than other drugs, although the difference was considerably smaller that means ADRs reported by diuretics was least among all other antihypertensives.

R. Sudhakar et al[18] studied for Adverse drug reaction associated with antihypertensive drugs and its management showed diuretics had the most common side effect of hyponatremia resulting into myalgia, weakness and lethargy which as well was a common reported ADR by diuretic users.

In study conducted by Haralambos Gavras et al[19] on angiotensin converting enzyme inhibitors properties and side effect mentioned a number of potential adverse reactions that are inherent in their mechanism of action. Hypotension is more profound and abrupt with the fast-acting captopril, which frequently produces a "triphasic response" characterized by an immediate blood pressure drop occurring within 20 to 30 minutes that is followed by an intermediate rise and a subsequent, more gradual fall over the next few days i.e. cardiovascular ADRs were most reported. But contrarily my study concluded maximum adverse reaction caused by ACE inhibitors was found to be on respiratory system.

In study by The National Institute for Health and Clinical Excellence (NICE) recommends that an ACE inhibitor or a 'low-cost' ARB is offered first line to patients under the age of 55[20] but as observed in my study the ADRs reported by ARBs (44%) was way high to consider it as single first line drug.

Calcium channel blockers (CCBs) are heterogeneous class of drugs which are the most commonly used antihypertensive drug[21,22]. My study found the most common ADRs caused were by CCBs as well implying most likely it to be most commonly prescribed AHA.

The most common CNS complaints are Dry mouth, headache and dizziness. Dry mouth and fatigue were the most common ADR caused by amlodipine and was the reason for discontinuation of medication. This finding is supported by the study of Ibn et al.

Concluded by my study among individual drugs amlodipine was found to be the commonest drug associated with ADRs with one third of total number of reported ADRs.

The most common systems associated with ADRs in our study were the CNS followed by CVS, respiratory and gastrointestinal system. Contrary finding with CVS being the most affected system was observed by Kumar et al[24]. The common complaints with the usage of amlodipine were Fatigue, dry mouth palpitation, dizziness, disturbed sleep pedal oedema and constipation. Oedema has been reported as the most common problem with amlodipine by Ramesh et al[25].

Among women, monotherapy with CCBs was associated with incidences of nocturia and voiding symptoms. Among men of all ages, positive associations were observed for thiazides and loop diuretics. This was found in study by Susan A et al. Present study found only similar 2 incidences with CCBs and no such ADR was found with any male patient.

A comprehensive review of literature on Beta-blockers and central nervous system side effects (2016) by Mc Ainsh J, Cruickshank JM[26] has shown that the incidence of CNS side effects such as sleep disturbances, dreaming, nightmares and hallucinations following clinically accepted doses of the beta-blockers under scrutiny is generally low and that effects on short-term memory are minimal or absent. This is in agreement with the pharmacokinetic observation of adverse drug reactions found in my study where ADRs reported were lesser than those by other AHA groups.

In study Authored by Michael Stewart, Reviewed by Sid Dajani in Apr 2018 under the title Prazosin an alpha blocker[27]. Constipation or diarrhoea, feeling sick Headache Feeling depressed or nervous, the sensation of having a 'thumping heart' (palpitations), blocked nose, dry mouth, rash, feeling shortness of breath, feeling the need to pass urine more frequently, swollen hands or feet are the common side effect of which dry mouth, dyspnea and palpitations were found to my study as well.

Conclusion

In the above pharmacovigilance study, it was found out that adverse drug reactions reported by the commonly used antihypertensives was least with the poly therapy as compared to monotherapy. Causality assessment was done using Naranjo's probability scale and more than

half of reported ADRs were classified as possible and on WHO-UMC more than half of them were probable. Hartwig severity assessment concluded all the ADRs were only, mild and more than 2/3rd were level 2 mild ADRs. AS found the polytherapy with antihypertensives was associated with minimum adverse effects and hence could be preferred over monotherapy considering all the other physical and medical status of patient under control.

This study is helpful in selection of appropriate medicine for antihypertensive patients, enhancing patient's adherence with the therapy by selecting medicines of lesser ADRs profile reducing unnecessary economic burden to the patients due to unwanted effects of therapy.

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