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Research Article

A PHARMACOVIGILANCE STUDY ON DRUGS USED IN THE TREATMENT AND MANAGEMENT OF HYPERTENSION IN TIRUPUR ZONE

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ABSTRACT

The main aim of this study was to evaluate the incidence of ADRs, the patients who are receiving or taking antihypertensive medications. ADR monitoring is an important part of post marketing surveillance which helps in generating data safety of medications. Main aim to ADRs monitoring is to the promoting rational use of drugs, safe use of medicines improving patient care, improving public health. This was a prospective, observational, voluntary reporting study. Study was conducted in and around Coimbatore. Samples are collected in all age group. We are taken support of 'Suspected Adverse Drug Reaction Reporting form from IPC to collect samples. A total of 34 adverse drug reactions were observed in hypertensive patients during the 3 months study. A high percentage of adverse drug reaction occurred in middle age and female patients. Combination therapy was high occurrence of adverse drug reaction as compared to immunotherapy. Cardiovascular adverse drug reactions constituted a major component, followed by gastrointestinal and respiratory complaints. Beta-blockers were the drug category associated with majority of adverse drug reaction, followed by angiotensin. The present evaluation has revealed opportunities or interventions especially or avoidable ADRs which will help in promoting safer drug use, information to the healthcare professionals. Improve the quality of patient care and educate to increase awareness.

INTRODUCTION

According to World Health Organisation (WHO) the ADRs can be defined as 'a response to a drug that is noxious and unintended and occurs at doses normally used in human or the prophylaxis, diagnosis, and treatment of disease, or modification of physiological function'.[1,2] ADR can also be defined as 'an appreciably dangerous or unpleasant reaction, resulting from an intervention the related to the use of medicinal products, which predicts hazard from future administration and warrants and prevent ion or specific treatment or alteration of dosage regimen, or withdrawal of product[3]. Hypertension is an important public health challenges in both economically developing and developed countries. In India Adverse Drug Reactions (ADRs) are considered among the leading cause of morbidity and mortality. Approximately 6% of hospital admissions are estimated due to ADRs and regarding 6-15% of hospitalized patients experience a serious ADR. When the Food and Drug administration (FDA) approves a new drug or marketing, its complete adverse events profile may not be known because of the limitation of preapproval clinical trials.[4] Typically, clinical trials for new drugs are not short durations and are conducted in populations that number up to 5000, therefore, the most common dose related ADRs are usually detected in the pre-marketing phase while ADRs which are rare and those detected on long term use are not. A case in point is the development of brownish blue pigmentation o nails of a patient on atenolol for 3 years. Another patient on amlodipine for 8 years developed Schimberg's like purpuric pigmentation [5]

Classification of Adverse drug reaction[6,7]

Type-A (Augmented): Commonest (up to 70%)-Dose dependent, severity increases with dose. Preventable in most part by slow introduction of low dosages. Predictable by the pharmacological mechanisms, e.g., hypotension by beta-blockers, hypoglycemia caused by insulin or oral hypoglycemic, or NSAID induced gastric ulcers. Type-B

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(Bizarre): Rare, idiosyncratic, genetically determined, unpredictable, mechanisms are unknown, Serious, can be fatal; unrelated to the dose, e.g., hepatitis caused by halothane, aplastic Anaemia caused by chloramphenicol, neuroleptic malignant syndrome caused by some anaesthetics and antipsychotics. Type-C (Continuous drug use): Occurs as a result of continuous drug use. May be irreversible, unexpected, unpredictable, e.g., tardive dyskinesia by antipsychotics, dementia by anticholinergic medications. Type-D (Delayed): Delayed occurrence of ADRs, even after the cessation of treatment, e.g., corneal opacities after thioridazine, ophthalmopathy after chloroquine, or pulmonary/peritoneal fibrosis by methyserzide. Type-E (End of dose): Withdrawal reactions. Occurs typically with the depressant drugs, e.g., hypertension and restlessness in opiate abstainer, seizures on alcohol or benzodiazepines withdrawal; first dose hypotension caused by alpha-blockers (Prazosin) or ACE inhibitors. Type-F (Failure of therapy): Results from the ineffective treatment (previously excluded from analysis according to WHO definition), e.g., accelerated hypertension because of inefficient control. Since most trials exclude the elderly, children, pregnant women, patients with multiple diseases, and those on medication suspected of interaction with the study population may not be true representative of the real world where the drug is eventually used. [8] Hence, there is need to monitor the safety profile of all the medication on continuous basis and to review their therapeutic rationale in the light of add on information emanating out of Pharmacovigilance activities. Monitoring of ADRs is even more important in case of chronic ailments such as hypertension. More often than not, hypertension is an asymptomatic disorder and requires long term therapy predisposing to adverse drug event. Pharmacovigilance studies for monitoring ADRs relative to antihypertensive agents have been previously conducted by many workers in different parts of the world. [9-11]. A study conducted in the Indian capital reports that 22.3% of the patients experienced ADRs.[12] Another report on ADR monitoring in northern India mentions that 5.% of all visits to the medical department are drug related, and ADRs accounted for 45% of events. The patient's record was assessed and those who discontinue their antihypertensive therapy during the study period were enrolled and then evaluate the reason for discontinuation of therapy. A total of 1164 patients were record and prescribed with different classes of antihypertensive drugs. [13] Most common prescribing group was diuretics (30.4%), and second most common prescribing group was angiotensin converting enzyme inhibitors (ACEIs) (29.1%) [14]. Among ACEIs majority of cases were noted in dry cough in captopril users and in lisinopril. Among Calcium channel blocker, the most common adverse effect was headache in nifidipine user while bradycardia was noted in atenolol user. While among the users of diuretics, the most common adverse effects are hyperkalemia, hyperuricemia and dehydration. Moreover telmisartan in those patients cause adverse effects were swelling of ankle [15]. The study is aimed to evaluate the incidence of ADRs in patients receiving antihypertensive agents in Coimbatore. The ADR reporting is primarily based on drug categories, but sex, age, and weight have also been included as explanatory variables. The present work was an open, non-comparative, observational study to monitor ADRs associated with antihypertensive medicines in Coimbatore. The data was recorded on a questionnaire based Suspected Adverse Drug Reaction reporting (ADRM) form of Indian Pharmacopeia commission which is related to patient demographics (name, age, sex, weight, suspected adverse reaction, past medical history, present drug treatment, description , assessment and treatment of ADR. The study was conducted between December 2016 to June 2017 by an informed consent form was taken from the patients participating in the study. All newly diagnosed and old patients receiving antihypertensive medications irrespective of age sex were included in the study. All mentally compromised or unconscious patients and patients unable to respond to verbal questions were excluded from the study. All drug-related adverse events were evaluated according to the "IPC of Suspected Adverse Drug Reaction form" [16].

MATERIALS AND METHODS

Spontaneous reporting and intensive monitoring are the most suitable methods in clinical/hospital set up. The study was design a prospective, observation, voluntary reporting study. The study was carried out in and around Tirupur zone. This study was based on those patients who experienced on adverse reaction to medicine use, either during their stay in hospital or outside the hospital and visited the outpatient department and ultimately reported to clinical pharmacist.

Inclusion criteria*:* Patients with ADR, of any age of either sex, has of reported to the clinical pharmacist from outpatient department of Tirupur zone.

Exclusion criteria*:* The ADR that due to Medication errors, over prescribing, over dosing/excess consumption, drug-drug interaction, drug-food interaction, drug interaction with a use of alternative system of medicine. This study was carried out for a period of 06 months from December 2016 to June 2017. The data for the study was collected from the patients who had an ADR by personal interview. There were Personal interview with the clinical pharmacist or reporting person. Past history of medication use, which are generally obtained from past prescription.

RESULT

A total of 15 ADRs were observed in 58 hypertensive patients (73% male and 26% female) during the four month of study with a mean age of 51.52±12.1. A higher percentage of ADRs occurred in males 20 (58.8%) than females 14 (41.2%). A total of 15 ADRs (25.8%) were observed in the observed patient group. Of the 15 ADRs, 10 (66.6%) were mild, 5 (33.3%) moderate and only 1 (6.6%) was classified as severe (generalized weakness with metoprolol (100 mg) and another developed severe hypotension (B.P. 90/59 mmHg) with atenolol (50 mg). Among the organ systems affected, cardiovascular ADRs constituted a major component, followed by gastro intestinal complaints and respiratory complaints. Among 58 patients a total of 7 patients were given with diuretics about 71.4% of patients were experienced ADRs of Hyponatremia and hypokalemia. In angiotensin converting enzyme inhibitor (ACE inhibitors) enalapril and ramipril is most common prescribing drugs, about 66.6% of patients having dry cough. Angiotensin II receptor antagonist telmisartan and olmesartan are prescribed. In this about 75% of patients were experienced by the ADR.

Table 1 Adverse Drug Reactions and Therapeutics Class of Suspected Medication

Antihypertensive agents	Suspected ADR	Total no. of patients with ADR	Percentage of ADR in patients
Diuretics Furesimide	Hypotension Dry Cough	0 0	0 0
Hydrochlor thiazide	Hyponatremia-2 Hypokalemia-3 Total	5/7	71.4%
Angiotensin converting enzyme inhibitor Enalapril Ramipril	Dry cough Dry cough -2 Total	2/3	0 66.6%
Angiotensin II receptor antagonist Telmisartan	Dry cough -3 Hypotension-2 Bradycardia-1 Total	6/8	75%
Olmesartan	Cough - 2 Muscle cramp - 3 Dizziness -2 Total	7/8	87.5%
Calcium Channel Blockers Amlodipine	Pedal edema-2 Headache-2 Abdominal pain-2 Swelling of face-1 Giddiness-1 Total	8/10	80%
Nifedipine	Bradycardia- 2 Total	2/4	50%
Bete-blockers Metoprolol	Hypotension-2 Giddiness-1 Headache-0 Bradycardia-1 Total	4/6	66.6%
Nebivolol	Impotence -0 Bronchospasm- 0 Irritation over whole body - 1 Pedal edema – 0 Total	1/3	33.3%
Combination therapy Nebivolol + hydrochlor thiazide	Headache Pain in legs Postural hypotension Total	2/4	50%
Telmesartan + hydrochlorthiazide	Dizziness Lightheadache -1 Blurred vision-2 Total	3/6	50%
Amlodipine +atenolol	Hypotension -1 Muscle cramp -2 Bradycardia -1 Headache -0 Total	4/5	80%
Olemesartan + hydrochlortiazide	Dry cough - 2 Joint pain -0 Spinning sensation -1 Total	3/5	60%

In calcium channel blockers amilodipin and nifedipin causing ADRs such as edema, headache, giddiness bradycardia about 50% of patients were experienced by these ADR. betablockers such as metoprolol and nebivolol are prescribed drugs 49.9 % of patients were experienced ADRs such as hypotension, giddiness, bradycardia. About 60% of patients were experiencing a ADRs in combination therapy of nebivolol + hydrochlorthiazide (50%), telmesartan + hydrochlorthiazide (50%), amlodipine + atenolol(80%) and olemesartan+ hydrochlortiazide (60%).

DISCUSSION

ADRs can have a determinant effect on a patient's wellbeing and the overall health care system. A comprehensive daily ADR program in a hospital can help to 'complement organizational risk management activities, assess the safety of drug therapies, ADR incidence rates over time and educate health care professionals of drug effects and increase their level of awareness regarding ADRs o new and old drugs'[16,17]. The most commonly identified ADR was peripheral oedema due to amlodipine. Calcium channel blocker (CCB) related oedema is caused by preferential arteriolar or pre-capillary dilation without commensurate dilation in the venous or post-capillary circulation. Correction of oedema was done by physician with dose reduction or drug withdrawal.[18]. The second most common ADR was ACE inhibitors induced dry cough. Cough may occur within hours of first dose of medication, or its onset can be delayed for weeks to months after the initiation of therapy. The prevalence of ACE inhibitor-induced cough has been reported to be 5-35% in patients treated with these agents [19]. Women, individuals with ACE genotype II, and those of black or Asian ethnicity have been reported to be at increased risk of ACE inhibitor-induced cough[20]. Angiotensin II Receptor blockers (ARBs) confer many of the same hemodynamic benefits as ACE inhibitors, but these do not directly inhibit ACE activity or inhibit the breakdown o bradykinin[21]. ARBs should be acceptable substitute or ACE inhibitors in patients who have adverse events such as Kinin- mediated cough [22]. The classification of ADR's studies most reported in the published article as Type A and Type B. In present studies we got type A reactions as 30% and type B reactions as 70%. Most o the ADRs are unpredictable and not a dose dependent (Type B) found in our studies. In our study, the female hypertensive population was found to be more susceptible to ADRs than the one. Most of the ADRs were mild or moderate only a couple of cases of ADRs were severe as the patients suffered from severe hypotension and needed to be hospitalized. [23] The result confirms previous reports that the occurrence of ADRs is on higher side in females.[24] Though according to a recent survey, the overall tolerability of low to moderate dose antihypertensive medicines is likely to be similar in men and women. An expected, combination therapy was associated with higher number of ADRs as compared to monotherapy. [25] Amlodipine and atenolol combination therapy leads to greater risk of ADRs than the monotherapy as reported earlier [26]. In this study we found that CCB s were the commonest group of drugs prescribed, though the beta-blockers and ACE inhibitors were associated with higher incidence s of ADRs.[26] Our findings corroborate the results of previous studies which mention beta-blockers as the drug category most often

implicated with ADRs. Hence need to review the status of beta-blockers in management of hypertension. Recent prescribing patterns also suggest preferential use of CCBs (31.7%) over beta-blockers (7.5%) [27].

CONCLUSION

Such studies enables in obtaining information on the incidence and pattern of ADRs in the local population. The present evaluation has revealed opportunities for interventions especially or the avoidable ADRs which will help in promoting safer drug use in institutions. Similar data evaluation needs to be followed by dissemination o the information to the healthcare professionals, which helps to improve the quality of patient care by ensuring safer use of drugs. Similar reporting programs are necessary to educate and to increase awareness about reporting of ADRs among the healthcare professionals in the all the hospital in India

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