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

Muthukumar A¹*, SundaraGanapathy R², Suganthi S³, Ramu T⁴ and Mohan S³

¹²Faculty of Pharmacy, Karpagam University, Karpagam Academy of Higher Education, Coimbatore-21, Tamil Nadu, India
³Karpgam College of Pharmacy, Othakkalmandapam, Coimbatore-32, Tamilnadu India
⁴Sri Vinayaga Hospital and Diabetic Care, College Road Tirupur-02, Tamilnadu India

DOI: http://dx.doi.org/10.24327/IJRSR.2017.0805.0302

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. 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 of 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
Muthukumar A et al., A Pharmacovigilance Study on Drugs Used In The Treatment And Management of Hypertension In Tirupur Zone

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 by the ADR. Telmisartan and olmesartan are prescribed. In this about 75% of patients were experienced by the ADR.
Angiotensin II receptor blockers (ARBs) confer a higher risk of ADRs than the monotherapy as reported earlier. 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 a higher risk of ADRs than the monotherapy as reported earlier. 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].

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 a higher risk of ADRs than the monotherapy as reported earlier. 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 ANTAGONISTS

ANGIOTENSIN II RECEPTOR ANTAGONISTS

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               |               |                               |                              |
| Furosemide             | Hypotension   | 0                             | 0                            |
|                        | Dry Cough     | 0                             | 0                            |
| Hydrochlor thiazide     | Hyponatremia-2| 5/7                           | 71.4%                        |
|                        | Hyponatremia-3| Total                         |                              |
| Angiotensin converting enzyme inhibitor |               |                               |                              |
| Enalapril              | Dry cough     | 2/3                           | 66.6%                        |
| Ramipril               | Dry cough -2  | Total                         |                              |
| Angiotensin II receptor antagonist |       |                               |                              |
| Telmisartan            | Dry cough -3  | 6/8                           | 75%                          |
|                        | Hypotension-2 | Total                         |                              |
|                        | Bradycardia-1 |                              |                              |
| Olmesartan             | Cough - 2     | 7/8                           | 87.5%                        |
|                        | Muscle cramp  | Total                         |                              |
|                        | - 3           |                               |                              |
|                        | Dizziness -2  |                               |                              |
| Calcium Channel Blockers |               |                               |                              |
| Amlodipine             | Pedal edema-2 | 8/10                          | 80%                          |
|                        | Headache-2    | Total                         |                              |
|                        | Abdominal pain-2 |                       |                              |
|                        | Swelling of face-1 |                   |                              |
|                        | Giddiness-1   | Total                         |                              |
| Nifedipine             | Bradycardia-2 | 2/4                           | 50%                          |
|                        | Total         |                               |                              |
| Bete-blockers          | Hypotension-2 | 4/6                           | 66.6%                        |
|                        | Giddiness-1   | Total                         |                              |
|                        | Headache-2    |                               |                              |
| Metoprolol             | Impotence -0  | 1/3                           | 33.3%                        |
|                        | Bronchospasm  | Total                         |                              |
|                        | - 0          |                               |                              |
|                        | Irritation over whole body - 1 |                   |                              |
|                        | Pedal edema – 0 |                   |                              |
| Neovibol               | Headache      | 2/4                           | 50%                          |
|                        | Pain in legs  | Total                         |                              |
| Combination therapy    | Postural hypotension | 2/4 | 50% | |
| Nebiviolol + hydrochlor thiazide | | Total | 3/6 | 50% | |
| Telmesartan +hydrochlor thiazide | | 3/6 | 50% | |
| Amlodipine +atenolol   | Hypotension -1| 4/5                           | 80%                          |
|                        | Muscle cramp -2 | Total                        |                              |
|                        | Bradycardia -1 |                               |                              |
|                        | Headache -0   | Total                         |                              |
| Olmesartan + hydrochlor thiazide | | 3/5 | 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. 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 a higher risk of ADRs than the monotherapy as reported earlier. 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 a higher risk of ADRs than the monotherapy as reported earlier. 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].

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 a higher risk of ADRs than the monotherapy as reported earlier. 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 a higher risk of ADRs than the monotherapy as reported earlier. 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 a higher risk of ADRs than the monotherapy as reported earlier. 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 a higher risk of ADRs than the monotherapy as reported earlier. 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].

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.[28] 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 of 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 all the hospital in India

Acknowledgement

We also express humble Thanks to Dr.T.Ramu, M.B.B.S Sri Vinayaga Hospital, Tirupur and S. Mohan M.Pharm, Ph.D, Principal of Karpagam College of Pharmacy

Reference

1. A Hussain, M Aquil, M S Alam, M R Khan. A pharmacovigilance study of antihypertensive medicines: Indian journal of pharmaceutical science, 2009; 71(3): 338-341
2. World health organization international drug monitoring: the role of national centres. Tech Rep Ser WHO 1972, No.498. Geneva: WHO.
3. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356:1255-9.
4. Upadayai JB, Nangai AK, Muija RD, Misra M, Mohan L, Sing KK. Cutaneous reactions due to antihypertensive drugs. Indian J dermatol, 2006;54:1255-33
5. Jose J, Rao GM. Pattern of Adverse drug reaction notified by spontaneous reaction in an Indian tertiary care teaching hospital Pharmacol Res, 2006;54:226-33
6. Venkaraddi magannavar chandrashekar, Allu Harikrishna ,Prassana kumar. Nambari Hemanthkumar. Adverse Drug Reaction monitoring and reporting: Indian journal of pharmacy practice, 2016; 9(1): 49-56.
7. Basak SC, Ravi K, Manavalan R, Sahoo K. A study of adverse drug reaction to antihypertensive drugs perceived by patients in a rural hospital. Indian J Pharm Sci, 2004; 66:814-817.
8. Ahmad SR. Adverse drug event monitoring at the food and drug administration. J Gen Intern Med, 2003;18:57-60
9. Riley, Wilton LV, Shakir SA. A post marketing observational study to assess the safety of mibefradil in the community of England. Int J Clin Pharmacol Ther 2002; 40:241-248.
10. Olsen H, klemetsrud T, Stokke HP, Treltis T, Westheim A. Adverse drug reaction in current antihypertensive therapy: A general practice survey of 2586 patients in Norway. Blood press, 1999; 8:94-101.
11. Wallender MA, Dimenas E, Svardsdik K, Wiklund I. Evaluation of three methods of symptom reporting in a clinical trial of fleodipin. Eur J Clin Pharmacol, 1991; 41:187-96.
12. Dhiakov V, Singh S, Anand KS. Adverse drug reaction monitoring in Indian Acad Clin Med 2004; 5:27-30.
13. Parhasarathi G, Olsson S, Adverse drug reaction. In: parhasarathi G, Nyfors-Hansen K Nahata MC, editors. A textbook of clinical pharmacy practice, 1 st ed. Chennai: orient lomman pvt ltd; 2004:84-102.
14. Garg KC, Singhal KC. Kumar S. Monitoring the adverse profile of atenolol a collaborative study. Indian J Physiol Pharmacol 1993; 37:213-216.
15. Uppsala monitoring Centre (WHO-UMC) System for standardised case causality assessment. Available from: http://who-umc.org/graphics/4409.pdf. [cited in 2006].
16. Sani Ibn Y, Tia F, Abdulgani G, Jamilu M Garba Tom. Evaluation of relative incidence of adverse effects leading to treatment discontinuation recommended antihypertensive drugs. Int Res J PARM’2013; 6:58-61.
17. Mudassar Iqbal Arain, Muhammed Ali Ghoto, Abdullah Dayio. Pharmacovigilance studies of antihypertensive medications in teaching hospital: Young Pharm, 2016;8(3): 259-265.
18. Vervoloet D, Durham S. ABC of allergie adverse reaction to antihypertensive drugs. Br Med J, 1998; 316:1511-4.
19. Caranasos G, Stewart RB, Cluff LE. Drugs induced illness and caused hospitalization. J Am Med Assn 1974; 228:713-7.
20. Alleig HW. Adverse reaction to antihypertensive therapy. Cardivas drug Ther, 1998;12:189-96
21. Lewis CE, Grandits GA, Flack J, MacDonalds R, Elmer PJ. Efficacy and tolerance of antihypertensive treatment to men and women with stage -1 diastolic hypertension study. Arch Intern Med 1996; 156:377-85.
22. Goldberd AI, Dunley MC, Sweet CS. Safety and tolerability of losartan potassium, angiotensin converting enzyme. Inhibitors for the treatment of systemic hypertension. Am J Cardiol, 1995; 75:793.
23. Akici A, Kalaka S, Ugrulu U, Hale Z, Toklu, Oktay S. Antihypertensive drug utilization at health centres in a district of Istanbul. Pharmacy world science, 2007; 29:116-21.
24. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A Meta analysis of prospective studies. JAMA. 1998; 279(15):1200-5.
25. Bates DW, Spell N, Cullen DJ, Burdick E, Laird N, Peterson LA. The cost of adverse drug reactions in hospitalized patients. JAMA. 1997; 277 (4):307-11.
26. Mandavi, Sanjay D’Cruz, Atul Sachdev. Adverse drug reaction & their risk factors: Indian J Med Res 136, 2012:404-410.
27. Suh DC, Woodall BS, Shin SK, Hermes-De-Santis ER. Clinical and economic event of adverse drug reaction in hospitalized patients. Ann Pharmacotherapy. 2000; 34(12):1373-9.