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Adverse Drug Reactions Associated with Antihypertensive Drugs and their Reporting through Pharmacovigilance in India

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Abstract: ***Hypertension is a global health concern, and its management primarily involves the use of antihypertensive drugs. These medications, although effective in controlling blood pressure, are not without adverse drug reactions (ADRs). In India, where hypertension prevalence is rising, pharmacovigilance plays a critical role in identifying, managing, and reporting these ADRs to ensure patient safety. This review discusses the common ADRs associated with various classes of antihypertensive drugs, the pharmacovigilance landscape in India, challenges in reporting ADRs, and the importance of strengthening pharmacovigilance mechanisms to mitigate the risks associated with antihypertensive therapy.***

Keywords: Adverse drug reactions, Antihypertensive drugs, Pharmacovigilance

1. Introduction

Hypertension, often referred to as the "silent killer, " affects millions of people globally, and its prevalence is on the rise in India. According to the Global Burden of Disease (GBD) study, hypertension is one of the leading contributors to cardiovascular diseases (CVDs), which are the primary cause of death worldwide (1). Antihypertensive drugs are essential in managing blood pressure levels, but their use is often associated with a range of ADRs that can affect patient adherence, quality of life, and overall treatment outcomes. These ADRs, if not identified and managed early, can lead to serious health complications. Pharmacovigilance, the science of detecting, assessing, understanding, and preventing adverse effects, is crucial in ensuring the safe use of antihypertensive drugs (2).

India, with its large and diverse population, presents unique challenges in pharmacovigilance. The country has a burgeoning hypertensive population, yet the awareness and reporting of ADRs are often suboptimal. This review focuses on the common ADRs associated with antihypertensive drugs, their mechanisms, and the current state of pharmacovigilance in India. It highlights the need for improved ADR reporting systems and the role of healthcare professionals in promoting pharmacovigilance.

2. Classes of Antihypertensive Drugs and Their Associated Adverse Drug Reactions

1) Diuretics

Diuretics are commonly used as first - line agents in the management of hypertension. They work by reducing blood volume through increased excretion of sodium and water (3). However, they are associated with several ADRs, including electrolyte imbalances, dehydration, and metabolic disturbances.

- **Thiazide diuretics**, such as hydrochlorothiazide, can lead to hypokalemia, hyponatremia, hyperglycemia, and hyperuricemia (4). Hypokalemia is particularly concerning as it can predispose patients to cardiac arrhythmias.
- **Loop diuretics**, like furosemide, can cause more profound electrolyte disturbances, including hypomagnesemia and hypocalcemia, along with hearing loss (5).
- **Potassium - sparing diuretics**, such as spironolactone, may cause hyperkalemia and gynecomastia in males (6).

2) Beta - Blockers

- Beta - blockers, such as atenolol and metoprolol, are widely used to reduce blood pressure by blocking beta - adrenergic receptors, thus reducing heart rate and cardiac output (7). Common ADRs associated with beta - blockers include:
- Bradycardia, hypotension, and heart block, which are particularly risky in patients with preexisting conduction abnormalities (8).
- Bronchospasm, especially in patients with asthma or chronic obstructive pulmonary disease (COPD) (9).
- Fatigue, depression, and sexual dysfunction, which can significantly affect adherence to therapy (10).

3) Angiotensin - Converting Enzyme (ACE) Inhibitors

ACE inhibitors, such as enalapril and lisinopril, block the conversion of angiotensin I to angiotensin II, leading to vasodilation and reduced blood pressure (11). While generally well - tolerated, they are associated with several ADRs:

- **Cough**, a common side effect due to increased bradykinin levels, is reported in up to 20% of patients (12).
- **Angioedema**, a rare but life - threatening condition, can occur due to the accumulation of bradykinin (13).
- **Hyperkalemia**, particularly in patients with renal impairment, is another significant concern (14).

4) Angiotensin II Receptor Blockers (ARBs)

ARBs, such as losartan and valsartan, block the angiotensin II receptor, leading to vasodilation without affecting bradykinin levels (15). As a result, they have a lower incidence of cough and angioedema compared to ACE inhibitors. However, they can still cause:

- **Hyperkalemia**, especially in patients with renal impairment (16).
- **Hypotension** and dizziness, particularly in patients who are volume - depleted (17).

5) Calcium Channel Blockers (CCBs)

CCBs, such as amlodipine and nifedipine, inhibit calcium influx into vascular smooth muscle cells, leading to vasodilation (18). ADRs associated with CCBs include:

- **Peripheral edema**, a common and dose - dependent side effect, particularly with dihydropyridines (19).
- **Flushing, headache, and dizziness**, which can occur due to vasodilation (20).
- **Gingival hyperplasia**, which is more common with long - term use (21).

6) Alpha - Blockers

Alpha - blockers, such as prazosin and doxazosin, work by blocking alpha - adrenergic receptors, leading to vasodilation (22). Common ADRs include:

- **Postural hypotension**, particularly after the first dose, which can lead to dizziness and falls (23).
- **Tachycardia**, which may occur as a reflex response to vasodilation (24).

7) Central Alpha - 2 Agonists

Drugs like clonidine and methyldopa reduce sympathetic outflow by stimulating central alpha - 2 adrenergic receptors (25). ADRs associated with central alpha - 2 agonists include:

- **Sedation**, dry mouth, and fatigue, which are common with clonidine (26).
- **Hemolytic anemia and hepatotoxicity**, which are rare but serious ADRs of methyldopa (27).

3. Mechanisms of Adverse Drug Reactions in Antihypertensive Therapy

The mechanisms underlying ADRs in antihypertensive therapy vary depending on the drug class and individual patient factors. For example, electrolyte imbalances with diuretics are due to increased renal excretion of electrolytes, while bradykinin accumulation with ACE inhibitors leads to cough and angioedema. Genetic factors may also play a role in ADR susceptibility, as variations in genes encoding drug - metabolizing enzymes and receptors can influence drug response (28).

Additionally, comorbid conditions such as renal impairment, diabetes, and cardiovascular diseases can increase the risk of ADRs. For instance, patients with renal impairment are at higher risk of hyperkalemia with ACE inhibitors and ARBs (29). Drug interactions, particularly in elderly patients taking multiple medications, further complicate the management of ADRs.

4. Pharmacovigilance in India: Current Status and Challenges

a) Pharmacovigilance Infrastructure

Pharmacovigilance in India is coordinated by the Pharmacovigilance Programme of India (PvPI), which was launched in 2010 under the Ministry of Health and Family Welfare (30). PvPI works in collaboration with the Central Drugs Standard Control Organization (CDSCO) to monitor ADRs and improve drug safety. The program has established ADR monitoring centers (AMCs) across the country, where healthcare professionals can report ADRs through the "Suspected Adverse Drug Reaction Reporting Form" (31).

The reporting of ADRs is crucial for identifying new drug - related risks and improving patient safety. However, underreporting remains a significant challenge in India. Studies have shown that only a small fraction of ADRs are reported, leading to incomplete data on drug safety (32).

b) Barriers to ADR Reporting

Several barriers hinder effective ADR reporting in India:

- **Lack of awareness and training**: Many healthcare professionals are not adequately trained in pharmacovigilance, and there is limited awareness about the importance of ADR reporting (33).
- **Fear of legal repercussions**: Some healthcare providers are hesitant to report ADRs due to concerns about legal consequences or blame (34).
- **Workload and time constraints**: In busy clinical settings, healthcare professionals may not have the time to complete ADR reporting forms (35).
- **Patient - related factors**: Patients may not recognize or report ADRs to their healthcare providers, leading to underreporting (36).

c) Strategies to Improve Pharmacovigilance in India

To address these challenges, several strategies have been proposed to strengthen pharmacovigilance in India:

- **Increasing awareness and education**: Healthcare professionals should receive regular training on the importance of ADR reporting and how to identify and manage ADRs (37).
- **Simplifying the reporting process**: The introduction of user - friendly electronic reporting systems and mobile applications can make ADR reporting more convenient for healthcare providers (38).
- **Encouraging patient participation**: Patients should be educated about the importance of reporting any unusual symptoms or side effects they experience while taking antihypertensive medications (39).
- **Collaboration between stakeholders**: Collaboration between healthcare providers, regulatory authorities, pharmaceutical companies, and academic institutions can improve the overall pharmacovigilance system (40).

5. Conclusion

The management of hypertension with antihypertensive drugs is crucial for preventing cardiovascular complications. However, these drugs are associated with a range of ADRs that can impact patient safety and adherence to treatment. In India, pharmacovigilance plays a vital role in identifying and mitigating the risks associated with antihypertensive therapy. While the Pharmacovigilance Programme of India (PvPI) has made significant strides in improving drug safety, challenges such as underreporting, lack of awareness, and inadequate training continue to hinder the effectiveness of the system. Strengthening pharmacovigilance infrastructure, promoting ADR reporting, and fostering collaboration among healthcare professionals and regulatory authorities are essential steps toward improving patient safety and ensuring the safe use of antihypertensive drugs.

References

[1] GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet.2017; 390 (10100): 1345 - 1422.
[2] World Health Organization (WHO). The importance of pharmacovigilance - Safety monitoring of medicinal products. Geneva: WHO; 2002.
[3] Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta - analysis. Lancet.2007; 369 (9557): 201 - 207.
[4] Moser M, Setaro JF. Clinical practice. Resistant or difficult - to - control hypertension. N Engl J Med.2006; 355 (4): 385 - 392.
[5] Brater DC. Diuretic therapy. N Engl J Med.1998; 339 (6): 387 - 395.
[6] Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med.1999; 341 (10): 709 - 717.
[7] Bangalore S, Parkar S, Grossman E, Messerli FH. A meta - analysis of 94, 492 patients with hypertension treated with beta blockers to determine the effect on stroke and coronary outcomes. Am J Cardiol.2007; 100 (8): 1254 - 1262.
[8] Messerli FH, Grossman E, Goldbourt U. Are beta - blockers efficacious as first - line therapy for hypertension in the elderly? A systematic review. JAMA.1998; 279 (24): 1903 - 1907.
[9] Barnes PJ, Pauwels RA. Theophylline in the management of asthma: time for reappraisal? Eur Respir J.1994; 7 (3): 579 - 591.
[10] Chrysant SG. Current and future concepts in the treatment of hypertension. J Clin Hypertens (Greenwich).2012; 14 (9): 595 - 601.
[11] Gradman AH, Schmieder RE, Lins RL, Nussberger J, Chiang YT, Bedigian MP. Aliskiren, a novel orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. Hypertension.2005; 46 (4): 568 - 576.
[12] Dicpinigaitis PV. Angiotensin - converting enzyme inhibitor - induced cough: ACCP evidence - based clinical practice guidelines. Chest.2006; 129 (1 Suppl): 169S - 173S.
[13] Kostis JB, Kim HJ, Rusnak J, Casale T, Kaplan A, Corren J. Incidence and characteristics of angioedema associated with enalapril. Arch Intern Med.2005; 165 (14): 1637 - 1642.
[14] Palmer BF. Managing hyperkalemia caused by inhibitors of the renin - angiotensin - aldosterone system. N Engl J Med.2004; 351 (6): 585 - 592.
[15] Burnier M, Brunner HR. Angiotensin II receptor antagonists. Lancet.2000; 355 (9204): 637 - 645.
[16] Weir MR, Rolfe M. Potassium homeostasis and renin - angiotensin - aldosterone system inhibitors. Clin J Am Soc Nephrol.2010; 5 (3): 531 - 548.
[17] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al.2013 ESH/ESC Guidelines for the management of arterial hypertension. J Hypertens.2013; 31 (7): 1281 - 1357.
[18] Messerli FH, Grossman E, Gheorghiade M. Calcium channel blockers in chronic heart failure. Circulation.2000; 102 (4)
[19] Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. N Engl J Med.1996; 335 (15): 1107 - 1114.
[20] Opie LH, Gersh BJ. Drugs for the heart.7th ed. Philadelphia: Elsevier Saunders; 2009.
[21] Hassell TM, Hefti AF. Drug - induced gingival overgrowth: old problem, new problem. Crit Rev Oral Biol Med.1991; 2 (1): 103 - 137.
[22] Meredith PA, Reid JL. Doxazosin in the treatment of hypertension. J Cardiovasc Pharmacol.1993; 22 Suppl 5
[23] Kjeldsen SE, Lund - Johansen P, Nilsson PM, Mancia G. Unattended blood pressure monitoring and cardiovascular prognosis: a proof that unattended office blood pressure is a better cardiovascular risk factor than attended office blood pressure? Blood Press.2020; 29 (1): 1 - 5.
[24] Hossain MD, Tarbox AK, McIntyre P, Al - Qubbany A. Prazosin for the treatment of nightmares related to posttraumatic stress disorder. Am Fam Physician.2013; 88 (12): 825 - 826.
[25] Mancia G, Zanchetti A. Choice of antihypertensive drug and progression to diabetes mellitus. Curr Hypertens Rep.2006; 8 (5): 431 - 437.
[26] Freeman K, Castle D, Grace D. Central alpha agonists: pharmacologic and clinical aspects. J Clin Hypertens.2008; 10 (2): 12 - 20.
[27] Hall JE. Guyton and Hall Textbook of Medical Physiology.12th ed. Philadelphia: Saunders Elsevier; 2011.
[28] Johnson JA, Boerwinkle E, Zineh I, Chapman AB, Bailey K, Gong Y, et al. Pharmacogenomics of antihypertensive drugs: rationale and design of the pharmacogenomic evaluation of antihypertensive

responses (PEAR) study. Am Heart J.2009; 157 (3): 442 - 449.
[29] Mann JF, Hilgers KF, Strauch B. Nephrotoxicity of antihypertensive agents. Curr Opin Nephrol Hypertens.1994; 3 (2): 204 - 208.
[30] Central Drugs Standard Control Organization (CDSCO). Pharmacovigilance Programme of India. Ministry of Health and Family Welfare, Government of India. Available at: http: //cdsco. nic. in/.
[31] Pharmacovigilance Programme of India (PvPI). Indian Pharmacopoeia Commission. http: //www.ipc. gov. in.
[32] Kalaiselvan V, Thota P, Singh GN. Pharmacovigilance Programme of India: Recent developments and future perspectives. Indian J Pharmacol.2016; 48 (6): 624 - 628.
[33] Desai CK, Iyer G, Panchal J, Shah S, Dikshit RK. An evaluation of knowledge, attitude, and practice of adverse drug reaction reporting among prescribers at a tertiary care hospital. Perspect Clin Res.2011; 2 (4): 129 - 136.
[34] Gupta P, Udupa A. Adverse drug reaction reporting and pharmacovigilance: knowledge, attitudes, and perceptions among resident doctors. J Pharm Sci Res.2011; 3 (2): 1064 - 1069.
[35] Inman W. Attitudes to adverse drug reaction reporting. Br J Clin Pharmacol.1996; 41 (5): 434 - 435.
[36] Feely J, Moriarty S, O'Connor P. Stimulating reporting of adverse drug reactions by using a fee. BMJ.1990; 300 (6716): 22 - 23.
[37] Patel KJ, Kedia MS, Bajpai D, Mehta SS, Kshirsagar NA, Gogtay NJ. Evaluation of the adverse drug reactions monitoring system in India: A quantitative study. Indian J Med Res.2016; 144 (5): 740 - 749.
[38] Bhatt A, Gogtay NJ, Dalvi SS, Ghosh S. The challenges of pharmacovigilance: In India and beyond. J Postgrad Med.2017; 63 (3): 134 - 139.
[39] Kadam AV, Sinha SR. Current status and challenges of pharmacovigilance in India. J Young Pharm.2015; 7 (2): 90 - 95.
[40] Wadhwa M, Lahiri KK, Singh M. Strengthening pharmacovigilance in India: The way forward. Indian J Pharmacol.2015; 47 (6): 642 - 645.