PHARMACOVIGILANCE STUDY OF ANTIHYPERTENSIVE DRUG BASED ON THEIR TOXIC EFFECT

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Abstract:

Pharmacovigilance plays an essential role in safeguarding the safety and effectiveness of pharmaceuticals, especially antihypertensive agents that are commonly utilized in the treatment of hypertension. This review seeks to evaluate the adverse drug reactions (ADRs) linked to antihypertensive medications, with particular emphasis on their toxicological effects. A thorough investigation of numerous studies and clinical reports has been conducted to pinpoint the prevalent ADRs and their repercussions on various physiological systems.

The examination indicated that calcium channel blockers (CCBs) are commonly linked to adverse drug reactions (ADRs), primarily influencing the central nervous system (CNS). Additional systems that are affected include the cardiovascular, musculoskeletal, gastrointestinal, respiratory, and dermatological systems. The results of this review emphasize the critical need for ongoing pharmacovigilance to identify, evaluate, and mitigate ADRs, ultimately improving patient safety and therapeutic results. Furthermore, this review highlights the importance of personalized medicine and the meticulous choice of antihypertensive treatments to reduce harmful effects and enhance treatment effectiveness.

Keywords: Pharmacovigilance, Anti- hypertensive, Adverse drugs reactions, Thalidomide.

Introduction:

The World Health Organization (WHO) characterizes pharmacovigilance as the discipline focused on the detection, assessment, understanding, and prevention of adverse drug reactions and other drug-related issues.(1) Pharmacovigilance encompasses a range of activities, including the identification, quantification, and documentation of drug-related problems that may lead to injuries. It serves primarily as a component of post-marketing surveillance, also known as phasefour studies, within the drug development process. The primary objectives are to quantify previously recognized adverse drug reactions (ADRs), uncover unrecognized ADRs, assess the effectiveness of medications in real-world contexts, and mitigate the mortality and morbidity associated with ADRs.(2) Additionally, national pharmacovigilance programs have been established to play a crucial role in enhancing public awareness regarding drug safety.(3)Pharmacovigilance is an ongoing process that involves the continuous monitoring and assessment of adverse events throughout the drug development process, ensuring the safety of participants and facilitating an ongoing evaluation of risks and benefits.(4)

Pharmacovigilance plays a crucial role in promoting the safe and appropriate use of medications by:

a) Encouraging the identification of previously unrecognized adverse drug reactions (ADRs) and interactions, as well as monitoring increases in the frequency of known ADRs.

b) Recognizing risk factors associated with the occurrence of ADRs.

c) Analyzing quantitative aspects of benefit-risk assessments and disseminating relevant information to enhance drug prescribing practices and regulatory measures.(5)

This review article elucidates the necessity and significance of pharmacovigilance in the daily practices of healthcare professionals, patients, and the pharmaceutical sector.

Importance of Pharmacovigilance:

The significance of pharmacovigilance lies in its role as a scientific discipline that addresses the intricate process of understanding and elucidating the nature of adverse drug reactions (ADRs) experienced by patients receiving oral, parenteral, or intravenous medications for various conditions. Medications available in the global market have undergone extensive testing, including clinical trials involving both animal and human subjects, to evaluate their safety for specific diseases and to identify potential side effects. However, a considerable number of ADRs remain undetected, with many being identified only through post-marketing surveillance. Research indicates that a substantial proportion of ADRs adversely affects patients' quality of life, prolongs hospital stays, and contributes to increased mortality rates. A pivotal study conducted by Lazarou in 1998 identified ADRs as the fourth to sixth leading cause of death in the United States, estimating that they account for 3-7% of all hospital admissions.(6) The primary aim of pharmacovigilance indicators is to establish metrics that facilitate the evaluation of

pharmacovigilance status, activities, and their effects across all tiers of the health-care system, ultimately to safeguard patient safety. The establishment of this comprehensive set of pharmacovigilance indicators will also yield objective benchmarks for measuring performance in this domain.

In summary, a collection of indicators focused on pharmacovigilance will:

- offer objective metrics to characterize the pharmacovigilance landscape within a country;
- evaluate pharmacovigilance activities at the global (national), regional, and health-care facility levels;
- assess the capacity for pharmacovigilance at these various levels;
- provide instruments for the oversight and monitoring of pharmacovigilance initiatives;
- evaluate advancements and facilitate the prioritization of efforts based on these evaluations;
- allow for the comparison of pharmacovigilance activities across different geographical regions and health facilities at specific points in time and over time.[7]

These activities are conducted with the objective of recognizing adverse events and comprehending, as much as feasible, their characteristics, occurrence, and possible risk factors. In essence, pharmacovigilance encompasses the identification and assessment of safety signals. A safety signal pertains to a concern regarding a higher incidence of adverse events than what would typically be anticipated in relation to the use of a product.[8]

Need of pharmacovigilance :

Humanitarian considerations highlight the lack of adequate safety evidence from clinical trials, particularly in animal studies and Phase 1-3 trials conducted before marketing authorization. While medications are intended to preserve life, succumbing to a disease may sometimes be inevitable; however, succumbing to a medication is intolerable. The costs associated with adverse drug reactions (ADRs) in a country often surpass the expenses of the medications themselves. It is essential to promote the rational use of medicines and ensure adherence, thereby fostering public trust. Ethically, it is wrong to withhold information about potential harm from individuals who are unaware of the risks.[9]A pharmacovigilance system is characterized as a framework employed by an organization to meet its legal obligations regarding pharmacovigilance, aimed at monitoring the safety of approved medicinal products and identifying any alterations in their risk-benefit profile. Additionally, a sufficient number of qualified and trained personnel must be available to carry out pharmacovigilance activities effectively.[10]

Significance of pharmacovigilance:

Pharmacovigilance is an evolving clinical and scientific field that plays an essential role in addressing the challenges associated with the expanding variety and potency of medications, including the unpredictable risks associated with vitamins. When adverse effects and toxicities arise, particularly those that are previously unrecognized, it is imperative that these incidents are reported, analyzed, and their implications communicated effectively to an informed audience capable of interpreting the data. there exists an inherent trade-off for all medications between their benefits and the potential for adverse effects. This risk can be mitigated by ensuring the rational use of high-quality, safe, and effective medicines while considering the expectations and concerns of patients during therapeutic decision-making. The objectives of pharmacovigilance include:

- Promoting public health and fostering trust among patients in the medications they utilize, which in turn enhances confidence in the overall health service;
- Anticipating and managing risks associated with drug use;
- Supplying regulators with essential information to update recommendations regarding medication use;
- Enhancing communication between healthcare professionals and the public;
- Educating healthcare providers on the effectiveness and risks of the medications they prescribe. This underscores the vital role of pharmacovigilance.[11]

Pharmacovigilance is primarily integrated into several key areas, notably the National Drug Policy. For every nation, the initial measure to guarantee the safety and rational utilization of medications involves the establishment of drug regulatory authorities equipped with robust pharmacovigilance programs. These programs are essential for monitoring and evaluating adverse drug reactions and for effectively communicating findings to pertinent stakeholders. In clinical practice, pharmacovigilance initiatives enable healthcare professionals to stay informed and updated regarding the adverse effects associated with medications. Many developing and underdeveloped countries face challenges due to poorly organized healthcare systems and a high prevalence of tropical infectious diseases, often affecting the same population simultaneously. Consequently, the administration of multiple medications in these regions frequently occurs without adequate consideration of potential adverse drug reactions or drug interactions. In such contexts, pharmacovigilance programs necessitate comprehensive training for healthcare professionals, thereby enhancing overall awareness of safe drug usage. Numerous international and national organizations offer valuable information and guidelines for the effective implementation of pharmacovigilance programs globally. These agencies serve as excellent resources for managing the risks linked to drug usage. The World Health Organization (WHO) maintains an extensive database that provides critical information on the effective implementation of pharmacovigilance, underscoring its significance as a vital tool for ensuring medication safety in public health.[12]

History of pharmacovigilance:

The etymology of the term “Pharmacovigilance” derives from the Greek word “Pharmakon,” meaning “drug,” and the Latin word “vigilance,” which translates to “to keep watch.” [13] The origins of Pharmacovigilance can be traced back 169 years to January 29, 1848, when a young girl named Hannah Greener from northern England tragically passed away following the administration of chloroform anesthesia prior to the excision of an infected toenail. Sir James Simpson had previously identified chloroform as a safer and more effective anesthetic, subsequently incorporating it into medical practice. An investigation was conducted to ascertain the circumstances surrounding Hannah’s death; however, the exact cause remained elusive. It is likely that she succumbed to either a fatal arrhythmia or pulmonary aspiration.[14]

Certainly, let us explore in greater detail the significant milestones in the evolution of pharmacovigilance.

1. Thalidomide Tragedy (1950s-1960s): Thalidomide, initially marketed as a sedative and antiemetic, resulted in severe congenital disabilities in numerous infants. This disaster highlighted the urgent need for systematic oversight of drug safety. The consequences of this event heightened awareness regarding the potential risks associated with pharmaceuticals, particularly during pregnancy.
2. Establishment of WHO Program (1968): In the wake of the thalidomide crisis, the World Health Organization (WHO) launched the International Drug Monitoring Program in 1968. This initiative established the groundwork for a worldwide network of pharmacovigilance centers, promoting collaboration in the collection and analysis of data related to adverse drug reactions (ADRs).
3. FDA and AERS (1970s): The Food and Drug Administration (FDA) introduced the Adverse Event Reporting System (AERS) in the 1970s. AERS became an essential instrument for gathering, managing, and analyzing information on adverse events linked to pharmaceuticals, allowing the FDA to oversee and regulate drug safety within the United States.
4. ICH Guidelines (1990s): The International Conference on Harmonization (ICH) significantly contributed to the standardization of pharmacovigilance practices on a global scale. ICH guidelines, including E2B, established a unified framework for the collection and sharing of safety data, enhancing international collaboration among regulatory bodies.
5. EU Pharmacovigilance System (2005): The European Union implemented a comprehensive pharmacovigilance system, reinforcing the monitoring and oversight of medicinal products. The European Medicines Agency (EMA) played a pivotal role in coordinating safety assessments and risk management strategies.
6. Periodic Safety Update Reports (PSURs): PSURs became a mandatory requirement for marketing authorization holders. These reports entail the regular submission of safety data

to regulatory authorities, ensuring ongoing evaluation of a drug's safety profile throughout its lifecycle.

7. Digital Era and Signal Detection (21st Century): The advent of technology has transformed pharmacovigilance practices, enabling more efficient signal detection and data analysis

8. Contemporary pharmacovigilance prioritizes international collaboration. Initiatives such as the WHO's global individual case safety reports (ICSRs) platform promote uniform reporting and the exchange of information among nations. This cooperative strategy engages regulatory bodies, pharmaceutical firms, healthcare practitioners, and patients in the oversight and assurance of the safety of medicinal products.(15)

9. 9. The United States Federal Food and Drug Act was enacted on June 30, 1906, establishing the requirement that drugs must be pure and free from contamination. Additionally, in 1911, this organization prohibited the false therapeutic claims associated with drugs.(16)

In 1937, the United States experienced 107 fatalities attributed to the consumption of sulfanilamide elixir, which utilized diethyl glycol as its solvent. This solvent was identified as the cause of the deaths; however, the manufacturing company was unaware of its toxic properties at that time. (17)

A significant transformation in European Pharmacovigilance occurred in 1961, prompted by the Thalidomide disaster. Dr. McBride, an Australian physician, penned a letter to the editor of the Lancet Journal, proposing a link between thalidomide and congenital malformations in infants. He noted that the rate of congenital malformations in babies rose from 1.5% to 20% among women who had ingested thalidomide during their pregnancies.(18)

Thalidomide was initially marketed as a sedative after extensive animal testing and was available as an over-the-counter (OTC) medication. It became widely used by pregnant women in various countries during the late 1950s and early 1960s to alleviate morning sickness.(19)

In India, the initiation of pharmacovigilance occurred in 1986. However, there was minimal growth despite the establishment of a formal Adverse Drug Reactions (ADR) monitoring system, which included 12 regional centers, each catering to a population of 50 million. In 1997, India participated in the World Health Organization's (WHO) ADR monitoring program based in Uppsala, Sweden, but this effort was unsuccessful. Consequently, the National Pharmacovigilance Programme (NPPV) of India, which receives support from the WHO and funding from the World Bank, became operational after 2005.(20)The commercialization of diacetylmorphine, later known as heroin, emerged as a significant issue in 1898, leading to widespread addiction by the early 20th century. In the United States alone, approximately 0.5 million individuals were identified as dependent on this substance. Thalidomide was introduced in 1957 as an over-the-counter hypnotic and sedative, later being prescribed to alleviate nausea in pregnant women. This was substantiated the following year when it was determined that thalidomide was responsible for 20% of the reported cases of phocomelia and limb agenesis.(21)

What is mean by hypertension:

Hypertension has been recognized by the World Health Organization (WHO) as a major contributor to morbidity and mortality on a global scale, accounting for approximately nine million deaths each year.[22] In the United Kingdom, the National Institute for Health and Care Excellence (NICE) defines high blood pressure, or hypertension, as a clinical blood pressure reading of 140/90 mmHg or higher, which must be confirmed by a subsequent average from ambulatory blood pressure monitoring during the day (or from home blood pressure monitoring) of 135/85 mmHg or above.[23]

Hypertension is characterized by an abnormal increase in either diastolic or systolic blood pressure; while mean arterial pressure is also elevated, it is not typically measured in individuals. Historically, greater emphasis was placed on diastolic values when diagnosing hypertension. However, it is now understood that elevated systolic pressure, referred to as "systolic hypertension," is linked to a higher risk of coronary and cerebrovascular diseases, such as stroke. Consequently, both systolic and diastolic pressures are now considered significant in clinical assessments.[24]

It Is important to note that high blood pressure is not exclusive to older adults; in 2015, over 2.1 million individuals under the age of 45 in England were reported to have high blood pressure.[25] Currently, hypertension is primarily identified by healthcare professionals through routine or opportunistic blood pressure assessments conducted in primary care settings.[26]Hypertension represents a global risk factor for the burden of cardiovascular disease and associated mortality.[27] It is often linked to various unhealthy behaviors, including smoking, poor dietary choices, obesity, excessive alcohol consumption, lack of physical activity, and sedentary occupational lifestyles. Additionally, an individual's awareness and perception of their hypertension play a crucial role in motivating changes in lifestyle and the adoption of healthier behaviors.[28]

In the United States, the prevalence of hypertension among adults was recorded at 31.9% based on the previous criteria (blood pressure ≥140/90 mmHg), whereas it has risen to 45.6% according to the 2017 ACC/AHA guideline definition (blood pressure ≥130/80 mmHg).[29]Hypertension is characterized by a persistent increase in blood pressure, which can lead to long-term damage to vital organs and is associated with higher rates of morbidity.[30]

History of hypertension:

The term essential hypertension, or 'hypertonie essential,' was first introduced in 1925 by physiologist Otto Frank to characterize elevated blood pressure without an identifiable cause. In 1928, physicians at the Mayo Clinic coined the term malignant hypertension to refer to a condition marked by extremely high blood pressure, severe retinopathy, and preserved kidney function,

which typically led to mortality within a year due to strokes, heart failure, or kidney failure.[31] As a result, hypertension was frequently categorized as either "malignant" or "benign." In 1931, John Hay, a Professor of Medicine at Liverpool University, remarked that there is merit in the assertion that the greatest risk for an individual with high blood pressure lies in its detection, as it often prompts misguided attempts to lower it.[32])

Common prescribed medicine for anti-hypertension:

HTN is treated with a variety of antihypertensive medications; The following classes are highly recommended for first-line treatment:

1.Thiazide-type diuretics

2.Calcium channel blockers

3.Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)

4.Alpha blocker

5. Beta blocker

Thiazide Diuretics:

Hypertension is usually first treated with thiazide and thiazide-like diuretics; In JNC8 guidelines, thiazide diuretics, alone or in combination with other antihypertensives, can be used as the firstline treatment for hypertonic hypertension (HTN) in people of all ages and race, unless there is evidence of chronic kidney disease for which angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker is prescribed[33]

The ALLHAT Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial suggested thiazide diuretics as the initial treatment for hypertension, unless there are contraindications|As a single agent, hydrochlorothiazide treatment at 12.5 mg or 25 mg daily has shown no evidence of reducing morbidity or mortality.[34]

Calcium Channel Blockers CCBs:

Calcium channel blockers (CCBs) have demonstrated a reduction in all cardiovascular events, with the exception of heart failure, akin to the effects of thiazide diuretics. They serve as the most suitable alternative to thiazides for patients who are unable to tolerate these diuretics.[35]

Calcium channel blockers (CCBs) can be categorized into two primary groups: dihydropyridines and non-dihydropyridines.

Dihydropyridines are recognized for their greater efficacy as vasodilators and are predominantly utilized in the treatment of hypertension. They exert a minimal impact on cardiac contractility and conduction, which makes them particularly suitable for managing high blood pressure. Nifedipine and amlodipine are among the most commonly prescribed medications within this category.In contrast, non-dihydropyridines are characterized by their reduced potency as vasodilators but offer enhanced effects on cardiac contractility and conduction. Consequently, they are more frequently employed as antiarrhythmic agents rather than for the treatment of hypertension.[36]

ACE inhibitors and ARBs:

ACE inhibitors and angiotensin receptor blockers (ARBs) are the preferred antihypertensive agents for individuals suffering from heart failure and chronic kidney disease. These medications are recommended as the initial treatment option for patients with chronic kidney disease who exhibit signs of proteinuria. Thiazide diuretics have been shown to be more effective than ACE inhibitors in reducing blood pressure and preventing strokes, while calcium channel blockers (CCBs) outperform ACE inhibitors in terms of lowering blood pressure and preventing both strokes and heart failure.[35]

Alpha-blockers:

Alpha blockers are not recommended as a first-line treatment for hypertension due to their lower efficacy in preventing cardiovascular disease compared to other first-line agents.[37]

Beta-blockers:

Beta-blockers are commonly associated with side effects such as bradycardia, constipation, depression, fatigue, and sexual dysfunction. Furthermore, these medications may lead to bronchospasm and exacerbate symptoms of peripheral vascular disease. They can also trigger a flare-up of Raynaud syndrome.[38]

ADR of that medication:

Thiazides Side Effects:

Thiazides and thiazide-like diuretics are linked to a variety of adverse effects. The majority of these effects are closely tied to the dosage of the diuretic; among them, hypokalemia and hyponatremia are the most frequently observed metabolic disturbances, followed by hyperuricemia, hypomagnesemia, hyperlipidemia, and elevated glucose levels.[39]

Calcium channel blockers:

The use of dihydropyridine calcium channel blockers (CCBs) frequently leads to the occurrence of peripheral edema. Long-acting nifedipine exhibits a greater frequency of edema in comparison to amlodipine; this edema is dose-dependent concerning the CCB. It is important to note that this condition is not associated with sodium or fluid retention, nor is it indicative of the development of heart failure.[40]

ACE inhibitors :

ACE inhibitors are frequently linked to mild hyperkalemia. The likelihood of hyperkalemia rises in individuals with renal failure, diabetes, or congestive heart failure, even among those with normal kidney function.[41] Ramipril and telmisartan exhibit comparable rates of hyperkalemia, acute kidney injury, and syncope. However, telmisartan is associated with a higher occurrence of symptomatic hypotension.[42]

Alpha- blockers:

Alpha-blockers are linked to tachycardia and orthostatic hypotension due to the dilation of veins.[43]

Beta blockers:

Beta-blockers are commonly associated with side effects such as bradycardia, constipation, depression, fatigue, and sexual dysfunction. Furthermore, these medications may lead to bronchospasm and exacerbate symptoms of peripheral vascular disease. They can also trigger a flare-up of Raynaud syndrome.[38]

Conclusion:

The pharmacovigilance study of antihypertensive drugs highlights the importance of continuous monitoring for adverse effects, as these medications can lead to various toxicities, including electrolyte imbalances, renal dysfunction, and cardiovascular complications. While these drugs are effective in managing hypertension, the study emphasizes the need for regular patient assessment and timely intervention to minimize the risks associated with their use. Vigilance in detecting, reporting, and analyzing adverse drug reactions is crucial to ensure patient safety and optimize therapeutic outcomes in hypertensive care.

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