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DIURETICS IN HYPERTENSION MANAGEMENT: ADVANCEMENTS THROUGH PRECISION MEDICINE

Yashika Bhatia[1], Md. Arqam[2], Preeti Gupta[3]* and Aseem Sethi[4]*

[1,2]Adesh Institute of Pharmacy and Biomedical Science (Adesh University), Bathinda 151101, Punjab, India.

[3]Department of Pharmacognosy, Adesh Institute of Pharmacy and Biomedical Science (Adesh University), Bathinda 151101, Punjab, India.

[4]Department of Pharmacy Practice, Adesh Institute of Pharmacy and Biomedical Science (Adesh University), Bathinda 151101, Punjab, India.

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***Corresponding Author**
Preeti Gupta
Department of Pharmacognosy, Adesh Institute of Pharmacy and Biomedical Science (Adesh University), Bathinda 151101, Punjab, India.
and
Dr. Aseem Sethi
Department of Pharmacy Practice,
Adesh Institute of Pharmacy and Biomedical Science (Adesh University), Bathinda 151101, Punjab, India.

ABSTRACT

One major worldwide health concern is hypertension, which has a substantial impact on cardiovascular morbidity and mortality. Medications, especially diuretics, have long been the cornerstone of hypertension management since they lower blood pressure and avert related problems. But new developments in precision medicine have completely changed the way diuretic therapy is administered, with personalized treatment plans based on each patient's unique genetic profile and biomarkers. Within the framework of precision medicine, this study examines the changing role of diuretics in the treatment of hypertension. Diuretics, which have distinct effects on renal physiology and electrolyte balance, are essential parts of hypertension therapy. These include thiazides, loop diuretics, and potassium-sparing medicines. As a result of multiple clinical trials and meta-analyses that have demonstrated their effectiveness in decreasing blood pressure, they are frequently recommended as first-line treatments in treatment guidelines. By using genomic data to customize diuretic medication to specific patient features, precision medicine introduces a paradigm change. Genetic differences affecting renal transporters, pharmacodynamic responses, and drug metabolism are becoming increasingly understood to be important predictors of treatment outcomes. Renal function markers and electrolyte levels

are examples of biomarkers that are used to improve patient-specific therapy algorithms, maximizing benefits and reducing side effects. Thanks to developments in genetic research, innovative diuretics with reduced side effects and increased therapeutic efficacy may now have viable targets. These advances hold the prospect of more precise therapies based on patient-specific genetic profiles, potentially addressing long standing difficulties associated with diuretic medication, such as electrolyte abnormalities and renal impairment. Moreover, the use of digital health technology enables instantaneous tracking of treatment reactions, augmenting therapeutic compliance and results for patients with hypertension. Despite these developments, there are still obstacles to overcome before precision medicine techniques may be widely applied in clinical settings. Significant obstacles still include concerns about cost-effectiveness, availability of genetic testing, and ethical issues with patient permission and data privacy. Nevertheless, in order to get past these obstacles and promote the incorporation of precision medicine into standard hypertension treatment regimens, there are continuing research projects and collaborative efforts involving clinicians, researchers, and policymakers. To sum up, diuretics continue to be essential in the management of hypertension, and precision medicine presents exciting opportunities to maximize their therapeutic advantages. The potential for a revolutionary shift in the management of hypertension toward safer, more efficient, and patient-centered care paradigms exists with the integration of genetic insights and customized treatment techniques. This abstract offers a thorough synopsis of the review paper, stressing the revolutionary role of precision medicine in enhancing the safety and efficacy profiles of diuretics and emphasizing their importance in the management of hypertension.

KEYWORDS: Diuretics, Hypertension, Precision Medicine, Pharmacogenomics, Biomarkers.

INTRODUCTION

The first-line treatment for many non-cardiovascular and cardiovascular disorders is diuretics. Patients with a variety of kidney issues, heart failure, edema, and hypertension are frequently treated with traditional diuretics. Heart and kidney disorders have a high death rate, and the number of people with these conditions rises annually. There is a generally positive risk/benefit balance when using various kinds of diuretics that are now accessible for therapeutic usage.[1] The most frequent cause of adult office visits to doctors and prescription drug use worldwide is the treatment of hypertension.[2] Hypertension affects about 1 billion

people worldwide.[3] It is the most prevalent chronic ailment in the Department of Veterans Affairs (VA) healthcare system, impacting over a million individuals, with a prevalence of 37%. Research has consistently indicated that a large number of patients do not have appropriate blood pressure (BP) control, indicating a discrepancy between recommended hypertension practice recommendations and actual BP control.[4]

In addition to being a cause of CKD, hypertension also advances the disease.[5-7] The frequency and intensity of hypertension rise when eGFR falls.[8] Moreover, CKD and hypertension both function as separate risk factors for cardiovascular disease (CVD).[9]

Medicine aims to treat patients individually by taking into account their unique traits, as well as how they respond to various treatments for the same illness. We call this precision medicine[10], since it is acknowledged that every therapy is unique and that precision in diagnosis and treatment is what we want to achieve with modern clinical and laboratory instruments.[11]

Increasing sodium excretion in the urine is a sensible and essential component of hypertension management.[12] In keeping with this knowledge, diuretics are included in hypertension guidelines as one of three first-line antihypertensive treatments that are equally weighted, along with renin-angiotensin system (RAS) blockers and calcium channel blockers.[13-17]

The fact that diuretics are more frequently used in combination with other classes than as a first-line treatment in many countries makes it difficult to understand their role in the treatment of hypertension. Actually, recommendations for single-pill combinations and combination treatments are becoming more and more important.[18] The four main groups of first-line drugs are beta-blockers, calcium channel blockers, thiazide diuretics, and angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs). This is not surprising, as the multifactorial origin of hypertension suggests that the underlying mechanism and hereditary propensity for high blood pressure may vary in each individuals. Consequently, it makes sense to customize or personalize care to each patient's unique needs.[18] We shall reiterate in this review the role of diuretics as crucial first therapies for hypertension and talk about the patient categories who benefit from them the most. We will also go into the usage of diuretics in the era of precision medicine.

In order to give clinicians and researchers a complete resource, this article summarizes the available information and highlights the developments in precision medicine. To optimize the management of hypertension and improve clinical results, it will be essential to comprehend the complex interaction that exists between diuretics and specific patient features. The incorporation of precision techniques into hypertension treatment procedures marks a significant advancement in the pursuit of individualized healthcare as we approach the dawn of a new age in medicine.

Rationale of the personalized approach to hypertension: former approaches and new opportunities.

The intricate interactions that occur throughout time between physiological systems, environmental variables, and susceptibility genes define the pathophysiology of hypertension.[19] Numerous approaches of treating hypertension individuals on an individual basis have been put forth and explored. Recognizing a set of characteristics that may distinguish a patient's reaction is necessary for personalized therapy in hypertension. Therefore, in order to more accurately determine a patient's predisposition to a disease or provide tailored management of the disease, a contemporary approach to personalized treatment should take into account the use of diagnostic and screening techniques that take into account the unique molecular or risk profile of the individual patient.[20]

Classification of Diuretics

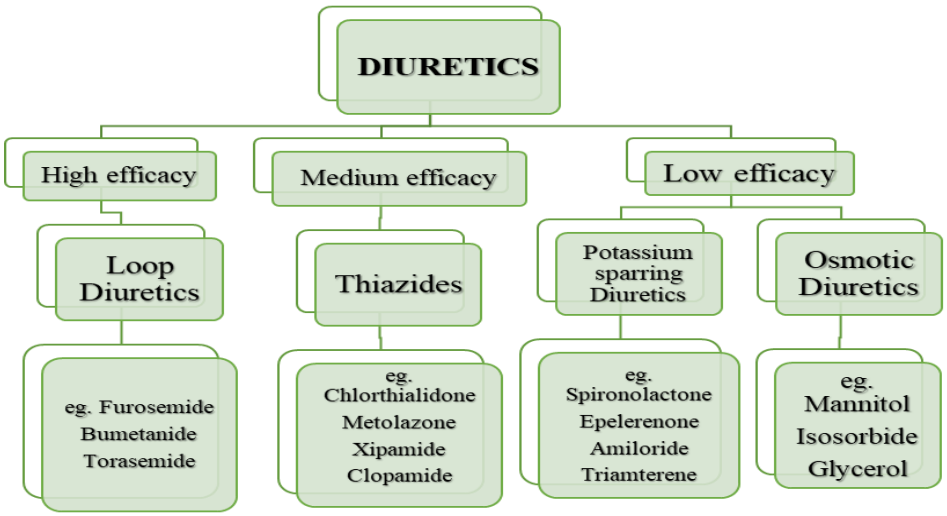

Figure 1: Classification of diuretics.

MECHANISMS OF ACTION OF DIURETICS

Thiazide Diuretics

Increased sodium and water excretion results from the inhibition of sodium reabsorption in the kidneys' distal convoluted tubule by thiazide diuretics, such as hydrochlorothiazide and chlorthalidone. Because of their efficiency and affordability, they are frequently suggested as the initial course of treatment for hypertension.[21]

Loop Diuretics

Bumetanide and furosemide are examples of loop diuretics that act on the ascending limb of the Henle loop. They are mostly utilized in individuals with heart failure, chronic renal disease, or severe hypertension since they are more potent than thiazides.[21]

Potassium-Sparing Diuretics

Potassium-sparing diuretics, like amiloride and spironolactone, function by directly blocking sodium channels in the distal nephron or by counteracting the effects of aldosterone. To avoid hypokalemia, they are frequently taken in conjunction with other diuretics.[21]

Carbonic Anhydrase Inhibitors and Osmotic Diuretics

Osmotic diuretics like mannitol and carbonic anhydrase inhibitors like acetazolamide have specific applications and are less frequently used in the treatment of hypertension in everyday life.[1]

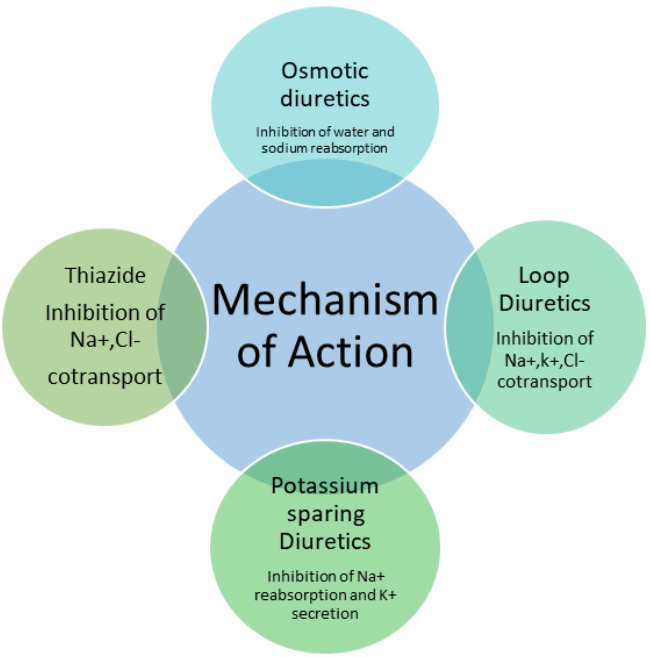

Figure 2: Mechanism of action of different diuretics.

Clinical Efficacy of Diuretics in Hypertension Management

According to hypertension recommendations, diuretics are one of three first-line treatment alternatives that are equally weighted. Increasing sodium excretion in the urine is the primary mechanism by which diuretics work, and this is a sensible and essential aspect of treating hypertension.[22] Numerous studies and clinical trials have established the clinical effectiveness of diuretics in the treatment of hypertension. Diuretics, such as potassium-sparing drugs, loop diuretics, and thiazides, efficiently reduce blood pressure by encouraging the excretion of water and salt, which lowers intravascular volume and peripheral vascular resistance.[23] Because thiazide diuretics, like hydrochlorothiazide, have been shown to reduce both systolic and diastolic blood pressure, they are frequently used as first-line therapies. They work especially well in mild to moderate hypertension and are frequently combined with other treatments to increase their effectiveness.[24]

Furosemide and other loop diuretics function at the ascending loop of Henle to cause fast diuresis, which makes them useful in treating diseases involving fluid overload or hypertension.

Potassium-sparing diuretics, like spironolactone, help patients who are at risk of electrolyte imbalances by reducing the potassium loss brought on by other diuretics.

Based on data from clinical trials, diuretics are generally quite effective at lowering blood pressure and lowering the risk of cardiovascular disease. This emphasizes their importance as key components of hypertension treatment plans.[25] Indeed, randomized control trials and meta-analyses have demonstrated that when compared with placebo or no treatment, blood pressure lowering by these antihypertensive drug classes is accompanied by significant reductions of stroke and major cardiovascular events.[9] A first-line treatment in Guidelines throughout the world list diuretics as one of the first-line treatments for patients with essential hypertension. This choice is based on the observation that a wide range of patients can benefit from diuretics, which counter the extracellular volume expansion and the salt retention associated with hypertension and reduce morbidity and mortality. For most patients, the risk of a clinically meaningful change in laboratory parameters is rather low, whereas the clinical benefits of diuretics are high. The American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines.[18]

Pharmacogenomics approaches in Diuretics

A crucial element of precision medicine is pharmacogenomics, the study of how a person's genes impact their reaction to medications. Individual reactions to diuretics can be influenced by variations in genes linked to the renal sodium transport and renin-angiotensin-aldosterone system (RAAS).[26] Pharmacogenomics investigates how a person's genetic makeup affects how they react to drugs, such as diuretics used to treat hypertension. By discovering genetic indicators that predict therapeutic efficacy, adverse effects, and ideal dosing regimens, this strategy seeks to tailor treatment.[27] Diuretic pharmacokinetics and pharmacodynamics can be strongly impacted by genetic differences in drug targets, transporters, and metabolizing enzymes. For example, variations in the genes that code for enzymes such as cytochrome P450 or transporters such as the thiazide-sensitive Na-Cl cotransporter (NCC) can affect how diuretics are metabolized and handled by the kidneys.

Pharmacogenomic testing can help select and dose diuretics in clinical practice to optimize therapeutic efficacy and minimize side effects. For instance, people with particular genetic profiles might benefit from diuretics more or need to take them at lower levels in order to obtain the best possible blood pressure control.[28] Genetic variations in the ACE or ENaC genes, for instance, may affect the efficiency and adverse effects of diuretics. Comprehending these genetic variables can aid medical professionals in anticipating which individuals will gain the most from particular diuretics, resulting in more individualized and efficient treatment regimens.[29]

Biomarkers: Key to Precision medicine

The goal of medicine is to treat each patient uniquely by taking into account their unique medical history, traits, and responses to various treatments. Precision medicine[10] refers to this since it is recognized that every therapy is unique and that precision in diagnosis and treatment is what we want to achieve using modern clinical and laboratory instruments.[30] Because they offer quantifiable markers of biological processes, disease states, or treatment responses at the molecular level, biomarkers are essential to precision medicine. Biomarkers such of renal function markers (e.g., estimated glomerular filtration rate), serum potassium levels, electrolyte levels, and genetic markers (e.g., polymorphisms in genes associated to diuretic metabolism or response) are important in the context of managing hypertension with diuretics.

By identifying patients who are more likely to experience side effects and forecasting individual responses, these indicators assist clinicians in customizing diuretic medication. For instance, serum potassium levels are monitored to inform adjustments to potassium-sparing diuretics, which helps avoid hyperkalemia, a common side effect. The incorporation of biomarkers into treatment algorithms improves therapeutic precision and enables customized interventions that maximize patient outcomes, safety, and efficacy in the management of hypertension.[30]

Since biomarkers are the chemicals that are now accessible within the field of omics sciences, they hold the key to precision medicine. While many of them are well-known to us from everyday life—creatinine, for example, is known to contribute to renal failure many biomarkers are relatively new and under scrutiny. This is often because of incorrect positioning, ignorance, or justifiable concerns about the costs versus benefits.[31]

Key Factors in Personalizing Diuretic Therapy

Treatment plans for personalized diuretic therapy are customized according to a patient's genetic profile, biomarkers, and other unique characteristics. This method requires thorough patient profile, which includes genetic testing, environmental assessments, and lifestyle evaluations. In order to maximize treatment effectiveness and reduce side effects in the control of hypertension, personalizing diuretic medication entails taking into account a number of important factors. Diabetic selection and dosage are influenced, first, by individual patient variables such as age, renal function, comorbidities (e.g., diabetes, heart failure), and concurrent drugs. Genetic diversity is important because specific genetic variations impact renal transport processes, medication metabolism, and diuretic response. By identifying these changes, pharmacogenomic testing can optimize treatment outcomes by customizing diuretic medication to each patient's genetic profile. Furthermore, indicators like blood pressure response, renal function markers like creatinine clearance, and electrolyte values like potassium aid in tracking the effectiveness of treatment and directing modifications. For example, in order to prevent electrolyte imbalances when treating potassium-sparing diuretics, serum potassium levels must be monitored.

Personalized therapy options are also influenced by clinical factors, including patient preferences, the degree of hypertension, and the existence of target organ damage. By incorporating these elements into a thorough treatment plan, diuretic medication is

guaranteed to be safe, well-tolerated, and successful in reducing blood pressure for each patient.

Patients with low-renin hypertension, for example, may respond better to thiazide diuretics, whereas patients with specific genetic abnormalities may need different treatments or dosages to prevent side effects.[32]

Adverse Effects and Management

Although diuretics are usually well tolerated, they can have unfavorable effects on the body, including dehydration, renal failure, and electrolyte abnormalities (hypo- or hyperkalemia). The likelihood of these negative consequences may be raised by genetic predispositions.[18] For instance, when using thiazides, patients with specific polymorphisms may be more prone to hypokalemia. Minimizing side effects requires regular monitoring of renal function and electrolyte levels in addition to dose adjustments based on individual risk factors.[33]

Future Directions in Diuretic Research and Precision Medicine

Diuretic therapy's future rests in incorporating precision medicine concepts even more. The goal of ongoing research is to find additional genetic markers and create more advanced prediction algorithms. Next-generation sequencing and sophisticated bioinformatics are examples of emerging technologies that will improve our capacity to treat hypertension on an individual basis. Future developments in precision medicine and diuretic research could lead to significant advancements in the efficacy and safety of hypertension treatment. The creation of new diuretics that specifically target renal transporters or pathways found through genomic and proteomic research is one important area of focus. These targeted treatments seek to minimize side effects including electrolyte imbalances while increasing the effectiveness of diuretics.

By discovering genetic markers that predict individual reactions to diuretics, further integration of pharmacogenomic methods is expected to improve individualized diuretic therapy. This involves utilizing genetic profiles to forecast possible bad effects, adjusting dosages, and selecting drugs optimally. Wearable technology and remote monitoring systems are examples of digital health technologies that are expected to be very important for tracking patient reactions to diuretic medication in real time. These technologies make it possible to continuously collect data on kidney function, blood pressure, and electrolyte levels. This allows for timely modifications to treatment regimens in order to get the best possible results.

Translating these discoveries into clinical practice also requires cooperation between researchers, physicians, and pharmaceutical corporations. Future diuretic medicines are anticipated to provide more accurate, tailored techniques that enhance patient adherence, outcomes, and the general standard of hypertension care by utilizing these advancement. Furthermore, the creation of innovative diuretics that specifically target genetic and molecular pathways has the potential to increase effectiveness and decrease side effects.[34-35]

Challenges and Ethical Considerations

The high expense of genetic testing and the requirement for substantial clinical validation are two of the many obstacles to implementing precision medicine in clinical practice. Since that not all patients may have access to cutting-edge diagnostic techniques, accessibility and equity are also issues. It is important to handle ethical concerns like informed consent and genetic privacy with great care. Notwithstanding these difficulties, precision medicine may be able to improve the course of hypertension, which makes it a worthy pursuit.

CONCLUSION

"The great physician treats the patient who has the disease; the good physician treats the disease," wrote Sir William Osler. As we get closer to the era of precision or stratified medicine, these remarks are extremely relevant. In summary, a revolutionary period in cardiovascular care has begun with the development of diuretics in the context of managing hypertension through the lens of precision medicine. Diuretics, which include potassium-sparing medicines, loop diuretics, and thiazides, are still considered core treatments because of their strong ability to lower blood pressure and lower the risk of cardiovascular events. However, by combining genetic insights, biomarker-guided tactics, and customized therapy algorithms, precision medicine has advanced these drugs beyond their conventional roles. Pharmacogenomics has made it possible to personalize medication based on genetic profiles by illuminating the genetic foundations of individual diversity in diuretic responsiveness. This strategy optimizes therapeutic outcomes and patient safety by reducing side effects and increasing treatment efficacy.

Research on diuretics will continue to focus on developing new medications that specifically target renal transporters linked to the pathophysiology of hypertension. With drugs made to target particular genetic and physiological markers, these advancements promise to broaden the therapeutic toolbox and provide specialized care for a range of patient populations.

Furthermore, there is a great deal of promise for improving the administration and tracking of diuretic medication through the integration of digital health technologies. Ongoing real-time data collecting enables proactive modifications to treatment plans, guaranteeing ideal blood pressure regulation and reducing the risk of electrolyte imbalances.

Translating scientific discoveries into clinical practice will require cross-disciplinary collaboration as these developments continue to emerge. Healthcare professionals may usher in a new era of individualized hypertension therapy that not only improves patient outcomes but also increases our understanding of the mechanisms underlying cardiovascular disease by embracing precision medicine approaches. In the end, the combination of diuretics and precision medicine holds the potential to completely rewrite the rules of care by providing individualized treatments that tackle the intricacies of hypertension with never-before-seen accuracy and effectiveness.

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