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CLINICAL PHARMACOLOGY OF ANTIHYPERTENSIVE DRUGS USED IN THE TREATMENT OF HYPERTENSION

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Abstract: This article provides an in-depth analysis of the clinical pharmacology of antihypertensive drugs commonly used in the treatment of arterial hypertension. The review covers the classification of antihypertensives, their mechanisms of action, pharmacokinetics, clinical indications, and safety profiles. Emphasis is placed on evidence-based therapeutic strategies, individual drug classes, combination therapy, and the personalization of treatment plans. The article also considers emerging therapies and pharmacogenomic perspectives relevant to modern hypertension management.

Keywords: Antihypertensive drugs, hypertension, ACE inhibitors, calcium channel blockers, beta-blockers, diuretics.

INTRODUCTION

Hypertension remains the leading modifiable risk factor for cardiovascular disease and premature death globally. Persistent elevation of arterial pressure contributes to the development of ischemic heart disease, stroke, chronic kidney disease, and heart failure. Effective pharmacologic intervention is crucial in reducing both systolic and diastolic blood pressure to target levels and minimizing target organ damage. A wide range of antihypertensive drug classes are available, each with distinct mechanisms, pharmacologic properties, and clinical profiles. This article reviews the pharmacodynamics and

pharmacokinetics of key antihypertensive drugs, their rational use in monotherapy and combination therapy, and their place in current treatment algorithms.

MATERIALS AND METHODS

ACE inhibitors — such as enalapril, lisinopril, and ramipril — inhibit the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, and reduce the degradation of bradykinin, promoting vasodilation. They lower systemic vascular resistance and aldosterone-mediated sodium retention.

ACE inhibitors are particularly effective in patients with hypertension coexisting with heart failure, diabetic nephropathy, or post-myocardial infarction. These agents are eliminated primarily by the kidneys and require dose adjustment in renal impairment. Adverse effects include dry cough (bradykinin-related), hyperkalemia, and, rarely, angioedema. They are contraindicated in bilateral renal artery stenosis and pregnancy.

RESULTS AND DISCUSSION

ARBs — such as losartan, valsartan, and telmisartan — block angiotensin II type 1 (AT1) receptors, preventing vasoconstriction and aldosterone release. Unlike ACE inhibitors, they do not affect bradykinin metabolism, resulting in fewer instances of cough or angioedema.

ARBs share most of the therapeutic indications of ACE inhibitors and are often used as alternatives in patients intolerant to ACE inhibitors. They have favorable metabolic profiles and are well-tolerated. Some agents, like telmisartan, offer long half-lives and once-daily dosing.

CCBs are divided into dihydropyridines (e.g., amlodipine, nifedipine) and non-dihydropyridines (e.g., verapamil, diltiazem). Dihydropyridines act primarily on vascular smooth muscle, causing vasodilation, while non-dihydropyridines also reduce heart rate and myocardial contractility.

CCBs are especially useful in elderly patients and those with isolated systolic hypertension. Amlodipine, with a long half-life (~30–50 hours), offers sustained blood pressure control with once-daily dosing. Side effects include peripheral edema, headache, and reflex tachycardia (especially with short-acting formulations). Non-dihydropyridines can cause bradycardia and should be avoided in heart block or heart failure with reduced ejection fraction.

Thiazide diuretics (e.g., hydrochlorothiazide, chlorthalidone, indapamide) act on the distal convoluted tubule to inhibit sodium reabsorption, reducing plasma volume and vascular resistance. They are recommended as first-line agents, especially in black or elderly populations.

Loop diuretics (e.g., furosemide) are reserved for hypertensive patients with fluid overload or renal impairment. Potassium-sparing diuretics (e.g., amiloride, spironolactone) are used in combination to mitigate hypokalemia or in resistant hypertension (e.g., spironolactone for aldosterone excess).

Adverse effects of diuretics include electrolyte imbalances (hyponatremia, hypokalemia), hyperuricemia, and glucose intolerance. Chlorthalidone may be more effective than hydrochlorothiazide due to a longer half-life.

Beta-blockers (e.g., atenolol, metoprolol, bisoprolol) reduce heart rate, cardiac output, and renin secretion via beta-1 receptor antagonism. They are indicated in patients with coexisting ischemic heart disease, arrhythmias, or heart failure with reduced ejection fraction [1].

Although less effective than other classes in preventing stroke in the elderly, beta-blockers remain important in specific comorbid conditions. Side effects include fatigue, bradycardia, bronchospasm (non-selective agents), and metabolic alterations (e.g., impaired glucose tolerance). Lipophilic agents like propranolol can cross the blood–brain barrier and cause CNS effects.

Combination therapy is often required to achieve blood pressure targets, particularly in patients with baseline systolic BP >20 mmHg above target. Fixed-dose combinations (e.g., ACE inhibitor + thiazide, ARB + CCB) improve adherence and have synergistic effects. Personalized therapy based on age, ethnicity, comorbidities, and pharmacogenetic profiles is increasingly emphasized in clinical guidelines (e.g., NICE, ACC/AHA).

Emerging tools such as renin profiling and genomic predictors (e.g., CYP2D6 and CYP3A5 polymorphisms) may eventually guide optimal drug selection and dosing, minimizing adverse effects and improving response.

Tailoring antihypertensive therapy to specific populations is a cornerstone of modern clinical pharmacology. In the elderly, for instance, isolated systolic hypertension is more prevalent due to arterial stiffening. In such cases, long-acting calcium channel blockers (e.g., amlodipine) and thiazide-like diuretics (e.g., indapamide) are preferred due to their favorable outcomes in trials like HYVET. However, overly aggressive blood pressure reduction in frail elderly patients may lead to orthostatic hypotension and falls, warranting individualized targets and slower titration [2].

In pregnancy, hypertension presents a complex pharmacological challenge. Many standard agents (e.g., ACE inhibitors, ARBs) are contraindicated due to teratogenic risks. Drugs such as methyldopa, labetalol, and nifedipine are considered safe and effective for gestational hypertension and preeclampsia. Methyldopa, a centrally acting alpha-2 agonist, is particularly notable for its long history of safe use, though it may cause sedation and depression with prolonged administration.

In black patients, studies have shown reduced efficacy of ACE inhibitors and beta-blockers when used as monotherapy, attributed to lower plasma renin activity. Instead, calcium channel blockers and thiazide diuretics are more effective in this demographic, as reflected in the ALLHAT trial. Such evidence supports a race-informed approach in first-line antihypertensive selection, while also promoting combination therapy when necessary.

Patients with chronic kidney disease (CKD) require careful management to both reduce blood pressure and preserve renal function. ACE inhibitors and ARBs are renoprotective in proteinuric CKD, but may increase serum creatinine and potassium, necessitating regular monitoring. Loop diuretics may be preferred over thiazides when glomerular filtration rate (GFR) falls below 30 mL/min [3].

Pharmacogenomics is increasingly recognized as a tool for optimizing antihypertensive treatment. Polymorphisms in genes such as CYP2D6 (affecting beta-blocker metabolism) or ACE (influencing response to ACE inhibitors) have been associated with variable therapeutic efficacy and adverse event risk. For example, patients with SLCO1B1*5 variants are more susceptible to statin-induced myopathy but may also exhibit altered pharmacokinetics of certain antihypertensives.

While pharmacogenetic testing is not yet routine in hypertension care, ongoing research supports its future integration, particularly for patients with drug intolerance or treatment-resistant hypertension. As polygenic risk scoring advances, clinicians may eventually predict both blood pressure responsiveness and long-term cardiovascular benefit from specific drug classes [4].

The timing of antihypertensive drug administration — a field known as chronopharmacology — has gained attention due to its impact on circadian blood pressure variation. Blood pressure follows a diurnal pattern, typically peaking in the morning and dipping at night. Non-dipping or reverse-dipping patterns, common in diabetics and the elderly, are associated with increased cardiovascular risk.

Clinical trials, such as the MAPEC and Hygia studies, suggest that evening dosing of at least one antihypertensive drug may restore nocturnal dipping, reduce 24-hour mean blood pressure, and significantly lower the risk of cardiovascular events. While these findings are promising, further validation in broader populations is required before universally changing prescribing practices.

Recent developments in drug formulation aim to improve adherence and therapeutic consistency. Sustained-release and extended-release formulations, such as nifedipine GITS (gastrointestinal therapeutic system), provide smooth 24-hour control with fewer peaks and troughs, minimizing side effects like hypotension or tachycardia [5].

Fixed-dose combination (FDC) therapy has revolutionized hypertension management by improving adherence, simplifying regimens, and offering synergistic blood pressure reduction. FDCs combining ACE inhibitors or ARBs with thiazides or CCBs are widely endorsed in guidelines as first- or second-line options, particularly in patients with baseline BP significantly above target.

CONCLUSION

Antihypertensive drugs represent a diverse class of pharmacological agents, each with unique mechanisms, therapeutic advantages, and safety profiles. A tailored approach to antihypertensive therapy — guided by clinical evidence, patient characteristics, and comorbidity profiles — is essential for optimizing outcomes in hypertension management. Combination therapy and newer pharmacogenomic tools offer further opportunities to enhance blood pressure control and reduce cardiovascular risk. Continued research and education are vital to promoting rational prescribing and improving adherence to treatment guidelines worldwide.

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