Antihypertensive Drugs

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Introduction

Hypertension or high blood pressure is one of the biggest single contributors to the global burden of disease and mortality. This common cardiovascular condition increases the risk for heart disease and stroke, which are two of the leading causes of death. High blood pressure prevalence worldwide is expected to increase over the next decade. Currently, about 1 of 3 US adults or about 94 million people have high blood pressure. Even though several antihypertensive drugs are available, only about half of the hypertensive patients have their high blood pressure under control.

Management of hypertension is crucial to prevent hypertension related diseases and death. A primary approach in hypertension management is lifestyle modification. Indeed, several epidemiological studies suggested that high blood pressure associated diseases and death could be significantly reduced through diet and exercise. Primary dietary modifications include the avoidance of diets high in sodium, fat and cholesterol. Lifestyle modification management for hypertension also includes reducing chronic exposure to environmental and occupational stress. In addition to lifestyle management, drugs are used to treat hypertension and reduce heart disease and strokes.

We will discuss the major antihypertensive drug classes that are currently available for the treatment and management of hypertension. A schematic description for the major antihypertensive drug classes is shown in Fig. 1. Major antihypertensive therapies and mechanisms of action will be discussed. These antihypertensive drugs can be used alone (monotherapy) or in combination to lower blood pressure.

Angiotensin System Inhibitor Drugs

Angiotensin system inhibitor drugs act by decreasing or blocking the actions of the hormone angiotensin II. The generation of the peptide angiotensin II is a multi-step enzymatic process. Angiotensinogen produced by the liver is converted to angiotensin I by the kidney generated enzyme renin. Angiotensin converting enzyme (ACE) located in the lung and endothelial cells converts angiotensin I to angiotensin II. Angiotensin II is a peptide hormone that causes vasoconstriction, increases sympathetic nervous system activity, and causes sodium retention that results in increased blood pressure and hypertension. Angiotensin system inhibitors include the ACE and renin enzymatic inhibitors that lower angiotensin II levels and angiotensin II receptor type 1(AT1) inhibitors that block angiotensin II actions. As a class of antihypertensive drugs, angiotensin system inhibitor drugs have been found to be safe and effectively lower blood pressure.

Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors such as lisinopril and captopril are among the most widely used antihypertensive drugs. The mechanism of action for ACE inhibitors is through decreasing angiotensin II generation. ACE inhibitors not only treat hypertension but also have important heart, brain, and kidney protective actions in hypertension and co-morbid conditions like diabetes. These ACE inhibitor

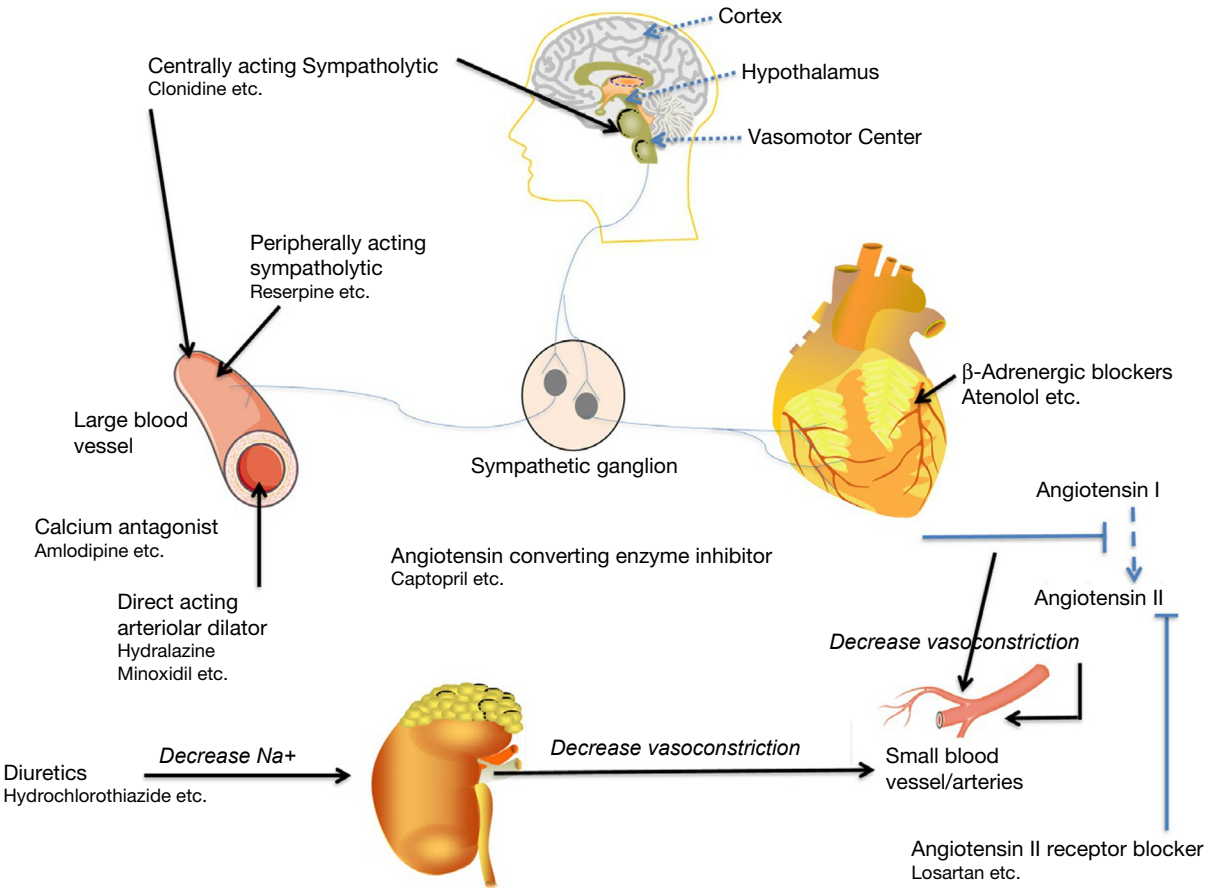

Fig. 1 Antihypertensive drug classes include angiotensin system inhibitors, diuretics, sympatholytics, and vasodilators. These drugs act on the kidney, brain, neurons, heart, and blood vessels to lower blood pressure in patients with hypertension. Servier Medical Art was used to generate the figure and is licensed by Servier under a Creative Commons Attribution 3.0 Unported License.

protective actions are related to the fact that high angiotensin II levels decrease organ blood flow, cause fibrosis, cause atherosclerosis, result in inflammation, and lead to cell death. Indeed, ACE inhibitors are widely use in treating hypertension in diabetic patients and patients with high cholesterol levels. ACE inhibitors provide strong beneficial effects in patients with heart failure, chronic kidney disease and in stroke patients. As with any drug, ACE inhibitors have side-effects. Side effects for ACE inhibitors include increased plasma potassium (hyperkalemia), dry cough, and an allergic reaction (angioedema). ACE inhibitors are contraindicated in pregnancy as they can cause fetal developmental defects.

Angiotensin Receptor Blockers (ARBs)

ARBs such as losartan and telmisartan work by selectively blocking AT1 receptor to exert their antihypertensive action. The binding of ARBs to block the AT1 receptor can be competitive or insurmountable. Several ARBs are pro-drugs and require conversion to a metabolite to produce their therapeutic action. Interestingly, ARBs can cause an increase in plasma renin, angiotensin I and angiotensin II levels by inhibiting the negative feedback action of angiotensin II on renin release. Elevated angiotensin II levels can act on unblocked vasodilatory and anti-fibrotic AT2 receptors to augment the therapeutic actions of ARBs. The primary therapeutic use for ARBs is as an antihypertensive drug to effectively lower blood pressure. Findings from several clinical trials have determined that ARBs are therapeutically useful in heart failure, postmyocardial infraction, and diabetic nephropathy. Clinical trials provide clear evidence that ARBs significantly reduce the incidence of stroke and new-onset diabetes. As far as side effects are concerned, occurrence of cough is less common in patients treated with an ARB than ACE inhibitor. Like ACE inhibitors, ARBs are contraindicated in pregnancy due to possible occurrence of fetal developmental defects.

Renin Inhibitors

The newest class of angiotensin system inhibitors is renin inhibitors such as aliskiren. These competitive enzymatic inhibitors block the conversion of angiotensinogen to angiotensin I to cause a decrease in angiotensin II levels. Renin inhibitors can cause an increase in plasma renin due to the lack of the negative feedback action of angiotensin II on renin release. Currently, aliskiren is the sole renin inhibitor approved for clinical use and effectively lowers blood pressure. Side effects are mild for aliskiren and like other angiotensin system inhibitors is not recommended in pregnancy.

Diuretic Drugs

Diuretic antihypertensive drugs act on the kidney to alter epithelial cell sodium and water transport to cause an increase in sodium and water excretion from the body. Increased sodium and water excretion from the body decreases extracellular fluid (ECF) volume and cardiac output resulting in decreased blood pressure. Long-term diuretic treatment will result in actions on blood vessels to decrease vasoconstriction resulting in a decrease in vascular resistance and blood pressure. Diuretic drugs are widely used, safe, and effectively lower blood pressure.

Thiazide Diuretics

Thiazide diuretics were discovered in the 1950s and found to be very effective orally active antihypertensive drugs. The mechanism of action for thiazide diuretics is inhibiting the apical sodium/chloride transporter in epithelial cells of the distal convoluted tubules to reduce ECF and cardiac output. Thiazide diuretics such as hydrochlorothiazide and indapamide are ideal first-line antihypertensive agent as proven through multiple clinical trials. In addition to lowering blood pressure, thiazide diuretics significantly reduce cardiovascular events and death without causing serious side effects. In certain hypertensive patient populations, such as patients with salt-sensitivity, obesity, and diabetes, thiazide diuretics act more effectively than other antihypertensive drugs. As with any drug, adverse effects are described for thiazide diuretics. Blood volume depletion, decreased plasma sodium (hyponatremia), decreased plasma potassium (hypokalemia), and increased plasma pH (alkalosis) are the reported prominent side effects for thiazide diuretics. Overall, low dose thiazide diuretics have demonstrated robust therapeutic efficacy and a high benefit-to-risk ratio in a wide range of hypertensive populations.

Loop Diuretics

Loop diuretics are the most potent diuretics that reduce ECF, cardiac output, and blood pressure. The mechanism of action for loop diuretics like furosemide is by inhibiting the apical sodium/potassium/chloride transporter in the thick ascending limb of the loop of Henle. Unlike thiazide diuretics, loop diuretics cannot be used as first-line antihypertensive therapy and use is limited in patients with kidney disease. Loop diuretics are very effective for edema in hypertensive patients due to their ability to act quickly and cause large reductions in ECF. Adverse effects for loop diuretics are like thiazide diuretics and include hyponatremia, hypokalemia, and alkalosis. One notable adverse loop diuretic effect is increased calcium excretion; hence, loop diuretics are not suitable for hypertensive patients with osteoporosis.

Potassium Sparing Diuretics

Diuretics that inhibit apical epithelial sodium reabsorption at the cortical collecting duct are the weakest class of antihypertensive diuretics. These diuretics spare potassium by preventing potassium secretion into the urine. There are two types of potassium sparing diuretics, aldosterone blockers and sodium channel inhibitors. Hyperkalemia is the major side effect for potassium sparing diuretics and limits their use as a stand-alone treatment for hypertension. Consequently, potassium sparing diuretics are not a first line antihypertensive drug; however, these drugs are used in combination with thiazide or loop diuretics to combat hypokalemia.

Amiloride and triamterene are two sodium channel inhibitors that act as potassium sparing antihypertensive diuretics. These antihypertensive drugs mechanism of action is by inhibiting the apical epithelial sodium channel that results in increased sodium excretion and reduces potassium excretion.

Aldosterone blockers like spironolactone and eplerenone are utilized to treat hypertension, particularly in patients with low renin and salt-sensitive forms of hypertension. The mechanism of action for these drugs is to inhibit aldosterone activation of mineralocorticoid receptors at the collecting duct resulting in changes in gene expression and the generation of proteins responsible for electrolyte transport. Aldosterone blockers have been found to be useful in preventing hypertensive end-organ damage, particularly heart and kidney. Clinical trials shown that spironolactone reduces heart damage and improve cardiovascular health in patients. Due to these beneficial actions the aldosterone blockers are often considered as the preferred combination treatment option in hypertensive patients with multiple comorbid conditions.

Nervous System Drugs

Increased sympathetic nervous system activity increases heart rate, vascular reactivity, and ECF to increase blood pressure. Sympatholytic drugs that act to decrease or oppose sympathetic nervous system activity effectively lower blood pressure. The early sympatholytic drugs were poorly tolerated due to severe side effects on the brain to cause mood disorders. Development of better sympatholytic drugs led to the development of adrenergic receptor antagonists that are effective antihypertensive drugs.

Central and Peripheral Sympatholytics

There are two types of antihypertensive sympatholytics, central sympatholytics and peripheral sympatholytics. Central sympatholytic drugs were first introduced into clinical use in the 1960s. These antihypertensive drugs like clonidine block sympathetic activity by binding to and activating central alpha-2 adrenergic receptors located within rostral ventrolateral medulla to reduce sympathetic outflow to the heart and blood vessels. Reduction in sympathetic out flow to the heart and blood vessels resulting in reduced cardiac output and vascular resistance to lower blood pressure. Peripheral sympatholytics are another type of antihypertensive sympatholytic drug. The mechanism of action for peripheral sympatholytics like reserpine is via neuronal and ganglionic blockade to reduce sympathetic outflow to decrease blood pressure. The clinical use for antihypertensive sympatholytic drugs are now very limited due to wide array of side effects on the brain and due to the increased availability of safer and more effective antihypertensive drugs.

Beta-Adrenergic Blocker

Beta-adrenergic blockers like propranolol and atenolol decrease heart rate and cardiac output by inhibiting heart beta-1 adrenergic receptors. Their use is particularly useful in hypertensive patients with cardiac complication like angina pectoris and arrhythmias. Beta-adrenergic blockers are more effective in young adults with hypertension because blood pressure is more dependent on cardiac output and can be used as a first-line antihypertensive therapy in this patient population. Beta-adrenergic inhibitors act on the kidney to decrease renin release and are also effective in hypertensive patients with high renin levels. In general, these antihypertensive drugs are used as second-line therapy in conjunction with ACE inhibitor or diuretics. Adverse effects can be related to beta-1 receptor blockade or non-selective beta-2 receptor blockade. Bradycardia (beta-1), lung bronchospasms (beta-2), and exercise intolerance (beta-1/beta-2) are side effects associated with beta-adrenergic blockers.

Alpha-Adrenergic Antagonist

In the pathophysiology of hypertension, increased sympathetic results in postsynaptic alpha-1 adrenergic receptor activation to increase vascular resistance and blood pressure. Selective alpha-1 adrenergic receptor antagonist act as an antihypertensive by blocking the postsynaptic noradrenaline vasoconstrictor effect to lower peripheral vascular resistance. Alpha-1 adrenergic receptor antagonist drugs like prazosin are effective antihypertensive drugs either alone or in combination with other antihypertensive drugs. Combination of alpha-1 adrenergic receptor antagonists and diuretics markedly enhances antihypertensive action. Apart from blood pressure lowering effects, alpha-1 adrenergic receptor antagonists demonstrate lipid lowering effects in hypertensive patients. In general, alpha-1 adrenergic receptor antagonists are well tolerated and there are no clinically significant adverse effects.

Vasodilator Drugs

Vasodilator antihypertensive drugs act on arteries to decrease vascular resistance and veins to decrease venous return and cardiac output. Although effective in blood pressure lowering, these vasodilator drugs activate several blood pressure counter regulatory mechanisms like sympathetic nervous system and renin-angiotensin system that are harmful for hypertensive patients. Consequently, these drugs are used to augment the pressure lowering effects of other antihypertensive drugs rather than as an initial first-line therapy.

Direct Vasodilators

The most common direct antihypertensive vasodilators are hydralazine and minoxidil. Hydralazine causes arterial relaxation by an unknown mechanism whereas minoxidil activates vascular smooth muscle K^+ channels to relax arteries. Hydralazine can be used as a long-term therapy for hypertension or as a short-term therapy for pregnancy-induced hypertension and hypertensive crisis. Minoxidil is limited to patients with severe hypertension unresponsive to other treatments. Nitric oxide donors such as nitroprusside and nitrates relax blood vessels by activating vascular smooth muscle cell guanylyl cyclase. Oral nitrates exert a relaxing effect primarily on veins and larger arteries. Nitrates are more widely used to treat angina or heart failure than as antihypertensive agent. On the other hand, nitroprusside acts on arterioles and lowers systemic vascular resistance when given intravenously. Nitroprusside is used in the intensive care setting to lower pressure in patients with severe hypertensive.

Calcium Channel Antagonists

In clinical medicine, the calcium antagonists or calcium-channel blockers were introduced in the 1960s and are now among the frequently prescribed drugs to treat cardiovascular diseases. The currently available calcium antagonists are chemically diverse; however, they share the common mechanism of action to block the trans-membrane flow of calcium ions through L-type voltage-gated channels. Calcium channel antagonists have therapeutic efficacy in patients with hypertension, angina pectoris, and cardiac arrhythmias. Chemically the calcium antagonists are two types, dihydropyridines like nifedipine and amlodipine and nondihydropyridines like verapamil and diltiazem. Calcium channel antagonists act on vascular smooth muscle cells to reduce intracellular calcium entry and lower vascular resistance resulting in a decrease in blood pressure. They also reduce the alpha-adrenergic receptor and angiotensin II vasoconstrictor actions that contributes to its antihypertensive action. As antihypertensive therapy, calcium channel antagonists are effective either alone or in combination with other antihypertensive agents. These calcium antagonist drugs are generally well tolerated but have side effects that include edema and tachycardia.

Further Readings

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