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Advances in Antihypertensive Drug Therapies: A Comprehensive Review of Mechanism, Efficacy, & Side Effects

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ABSTRACT

Hypertension remains a prevalent health concern worldwide, significantly increasing the risk of cardiovascular diseases. This comprehensive review provides a detailed examination of antihypertensive medications, encompassing their mechanisms of action, classification, and associated adverse effects.

The discussion begins with an exploration of risk factors contributing to hypertension, emphasizing the importance of lifestyle modifications in reducing susceptibility. Subsequently, the signs and symptoms indicative of elevated blood pressure are outlined to facilitate early detection and intervention.

The main focus of the review is on antihypertensive drugs, starting with diuretics, which act by promoting diuresis and sodium excretion. Thiazide, loop, and potassium-sparing diuretics are examined in depth, elucidating their pharmacokinetics and adverse effects.

Renin-angiotensin system inhibitors, including ACE inhibitors, ARBs, and direct renin inhibitors, are discussed next, emphasizing their role in regulating blood pressure and protecting target organs from hypertensive damage. The pharmacokinetic profiles and potential adverse effects of each class are thoroughly examined.

Sympathetic inhibitors, such as beta-adrenergic and alpha-adrenergic blockers, are then reviewed for their efficacy in mitigating hypertension through modulation of sympathetic pathways. Pharmacokinetic considerations and adverse effects are highlighted to guide clinical decision-making.

Finally, calcium channel blockers and vasodilators are explored for their vasodilatory effects and ability to reduce peripheral resistance. Pharmacokinetic properties and associated adverse effects are discussed to inform therapeutic management.

Overall, this review offers a comprehensive understanding of antihypertensive medications, providing clinicians with valuable insights into their mechanisms, classification, and adverse effects to facilitate optimal treatment strategies and improve patient outcomes in the management of hypertension.

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INTRODUCTION

High blood pressure, or hypertension, is treated with antihypertensive medications.[1] A dangerous medical disease known as hypertension is brought on by very high blood vessel pressure, which is often measured at 140/90 mmHg or more. The blood vessel pressure during a heartbeat or contraction is represented by the systolic pressure, whereas the blood vessel pressure during a heartbeat's intermission is represented by the diastolic pressure. [1,2]

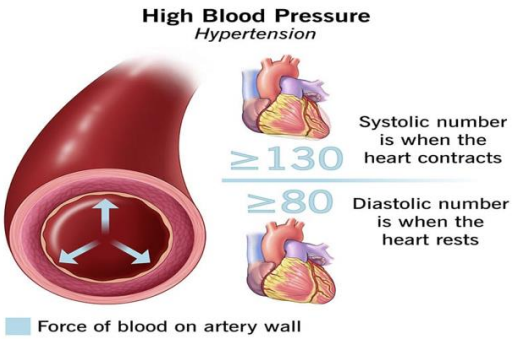

Fig 1: Hypertension Range

What are risk factors?

What do risk factors entail? High blood pressure can be caused by a variety of risk factors, including sex, race and ethnicity, age, family history, genetics, and bad lifestyle choices. Nonetheless, you can reduce your chance of acquiring high blood pressure by implementing healthy lifestyle practices.[2]

Fig. 2: Risk Factors Of High Blood Pressure

Signs and symptoms:

There is no doubt that hypertension causes a number of symptoms, such as headache, blurred vision, chest pain, dyspnea, and localized neurological impairments. Many people believe that these symptoms could be signs of elevated blood pressure.[3]

Fig. 3: Signs & Symptoms of Hypertension

Antihypertensive drugs:

Antihypertensive medications are important in treating high blood pressure, which is a major risk factor for many cardiovascular diseases, including heart attack, stroke, stroke, and heart failure. To protect your health and reduce your risk of contracting this dangerous disease, you need to control your blood pressure. Studies show that a drop in blood pressure of just 5 mmHg can reduce the risk of stroke by 34%, ischemic heart disease by 21%, and the risk of dementia, heart failure, and cardiovascular death by 10%. To avoid dangerous situations, you should take antihypertensive medications as recommended by your doctor and lead a healthy lifestyle.

Classification of antihypertensive drugs :

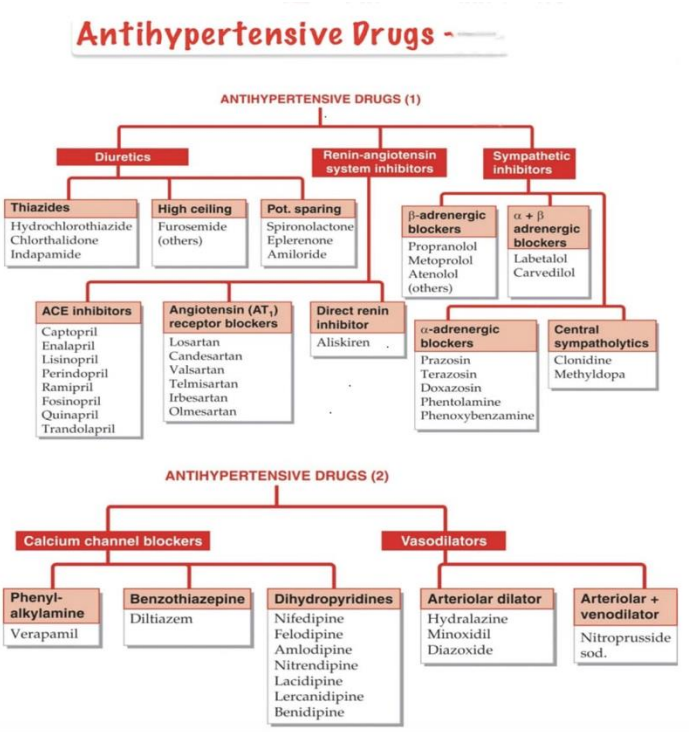

Fig. 4: Classification of Antihypertensive Drugs

Classification:

1) DIURETICS

Diuretics are an extremely effective class of medications that increase urination to remove excess water and electrolytes from the body. They are highly recommended for treating hypertension, also known as high blood pressure, which is a major contributing factor to heart disease. Prescription diuretics have been unequivocally proven to be highly effective in preventing heart attacks and strokes in many patients. Diuretics are widely used in clinical settings to manage edema and are considered the gold standard treatment for this condition. They work by reducing the reabsorption of sodium (Na+) in specific renal tubules, leading to an increase in urinary sodium and water excretion. The thick ascending limb of the loop of Henle reabsorbs around 25% of the Na+ from the glomerular filtrate. In comparison, the distal convoluted tubule reabsorbs approximately 5% of the Na+ through a thiazide-sensitive sodium-chloride (Na+-Cl-) co-transporter. It is essential to note that only about 1-2% of the Na+ ions are transported in the distal segment of the distal convoluted tubule and the collecting duct.

Types of Diuretics:

a) Thiazides diuretics

b) High ceiling/Loop diuretics

c) Potassium sparing diuretics

a) Thiazides Diuretics:

Thiazide diuretics work effectively on the distal convoluted tubule. They were discovered accidentally during experiments aimed at enhancing the carbonic anhydrase property. However, researchers found compounds that increase NaCl excretion instead of NaHCO3 secretion. Thiazide diuretics block the NaCl pump on the luminal side, which causes a relative deficiency of Na+ since the Na+K+ pump works overtime. This deficiency stimulates the Na+ Ca++ exchanger, leading to Na+ moving in, while Ca++ moves out, causing a deficiency of Ca++. However, under the control of PTH, Ca++ is reabsorbed. The greater the load of Na+ entering the tubules, the greater will be the loss of K+, Cl-, and H+. Additionally, Mg++ depletion occurs by some unknown mechanism.[9]

Examples:

1) Chlorothiazide

2) Chlorthalidone

3) Hydrochlorothiazide

4) Indapamide

5) Metolazone

Pharmacokinetics:

These drugs are oral diuretics, with Hydrochlorothiazide being the most commonly used prototypical drug. Chlorothiazide can also be administered in large doses. Chlorothiazide is slowly absorbed and has a duration of 24-74 hours. Metolazone is metabolized in the liver, however, it still reaches the kidneys in an unchanged form. Unlike loop diuretics, these drugs are administered in a single dose, which makes them a preferred choice for treating hypertension. [9]

Adverse effects:

It is crucial to note that thiazide diuretics can cause severe hypokalemia, which is a potentially deadly reduction in potassium levels in your body. Hypokalemia can lead to life-threatening heart rhythm abnormalities. To avoid this, your doctor may prescribe a potassium-sparing diuretic. Your healthcare team will closely monitor your potassium levels if you are taking these medications to ensure that you are safe and healthy. [8]

b) High ceiling/loop diuretics:

Loop diuretics, on the other hand, like furosemide, are a more potent form of diuretic medication that hinders the body's ability to reabsorb sodium at the ascending loop of the nephron, causing a substantial excretion of water in the urine [10]. Among various types of diuretics, loop diuretics are the most potent in inhibiting Na+ reabsorption, and they achieve this effect by targeting the thick ascending limb of the loop of Henle. [11]

Example:

1) Furosemide

2) bumetanide

3) torsemide

Pharmacokinetics: [12]

Due to their strong protein binding, loop diuretics have a small volume of distribution. Because loop diuretic molecules are protein-bound, for them to perform their function, they must be secreted along the luminal wall of the proximal convoluted tubules via several transporter molecules. Furosemide availability varies greatly; it might range from 10% to 90%. The absorption of furosemide into the bloodstream from the gastrointestinal system limits its biological half-life. Its excretion has an apparent half-life that is longer than its oral absorption half-life. Consequently, an intravenous dose of furosemide has twice the potency of an equivalent oral dose.

Adverse effect:

Furosemide is linked to three main categories of side effects: ototoxicity, hypersensitivity, hypovolemia and electrolyte imbalance brought on by diuresis. Excessive diuresis brought on by high doses of the medication may result in contraction alkalosis by reducing the volume of extracellular fluid. Patients using nonsteroidal anti-inflammatory medicines (NSAIDs), those with chronic kidney disease (CKD), and the elderly are more likely to experience this side effect. Numerous electrolyte abnormalities, such as hypokalemia, hypomagnesemia, hypocalcemia, hyponatremia, and hyperuricemia, can be brought on by furosemide. When giving furosemide to patients, it's critical to be aware of these adverse effects and keep a close eye on them. [13]

c) potassium-sparing diuretics:

Potassium-sparing diuretics are drugs that efficiently stimulate urine production without causing any loss of potassium in the urine. In a renal nephron, the reabsorption of sodium occurs primarily through the epithelial sodium channels (ENaCs) present on the luminal surface of principal cells lining the collecting tubules. This influx of positively charged Na+ into the cells during reabsorption creates an electronegative luminal environment, which prompts the secretion of potassium (K+) into the urine in exchange. [14]

Example:

1) Spironolactone

2) Eplerenone

Pharmacokinetics:
All potassium-sparing diuretics must be administered orally. Spironolactone undergoes metabolism in the gut wall and liver to form canrenone, which has a longer half-life and is undoubtedly responsible for the majority of the diuretic effect. The onset of action of spironolactone and eplerenone is slow, beginning after one day and reaching maximum effect in three to four days due to their transcriptional mechanism of action. Triamterene is extensively metabolized in the liver, and the diuretic effect is mainly due to tubular secretion of the sulfate ester metabolite. Amiloride is secreted unchanged into the proximal renal tubule, and both drugs have a rapid onset of action, making them highly effective. [15]

Adverse effect:
It is important to note that all potassium-sparing diuretics can cause hyperkalemia, which is an elevated level of potassium in the blood. There are specific groups of patients who are at a particularly high risk of developing hyperkalemia if they take these diuretics. These groups include patients with moderate to severe chronic kidney disease, hypoaldosteronism, and diseases that impair the body's response to aldosterone's potassium secretory effects. Elderly patients, those with chronic c kidney disease or diabetic nephropathy, and those with AIDS, or primary adrenal disease are particularly susceptible to hypoaldosteronism. [16]

2) Renin-Angiotensin System Inhibitors

The renin-angiotensin system "RAS" is an important element in the regulation of cardiovascular and renal function. RAS inhibitors should be prescribed as first-line therapy to treat hypertension, prevent heart failure, and reduce afterload. RAS involves a cascade of enzymatic reactions that include three components: angiotensinogen (Ao), renin, and angiotensin-converting enzyme (ACE), which produces angiotensin (Ang) II as a biologically active product. Masu. Ang II binds to two specific receptor types: angiotensin type 1 (AT1R) and type 2 (AT2R). They all belong to the family of heterotrimeric G protein-coupled receptors (GPCRs) with seven transmembrane domains. Most of Ang II's destructive effects are due to its interaction with AT1 receptors, which are the major receptors in adult tissues, whereas AT2 generally produces positive effects. Numerous classes of drugs have been developed that effectively block RAS at various levels, including inhibiting renin or ACE enzyme reactions, inhibiting Ang II synthesis, and abrogating the interaction of Ang II with AT1R. It has been. [17]

a) ACE INHIBITORS:

ACE inhibitors, such as lisinopril and captopril, are the most widely used antihypertensive drugs owing to their proven effectiveness in reducing high blood pressure [18]. Angiotensin-converting enzyme inhibitors unequivocally decrease angiotensin II production and increase bradykinin by effectively inhibiting its breakdown, thereby promoting vasodilation[19]. These drugs not only treat hypertension but also play a vital role in protecting the heart, brain, and kidneys in hypertensive patients with comorbidities like diabetes. This is because high levels of angiotensin II can cause decreased organ blood flow, fibrosis, atherosclerosis, inflammation, and cell death. [18]

Example:

1) Captopril

2) enalapril

3) lisinopril

Pharmacokinetics:
All ACE inhibitors bind to tissue and plasma proteins. Although the drug is eliminated relatively quickly by the kidney through glomerular filtration, it is important to note that binding to tissue sites results in a prolonged terminal elimination phase. It is worth noting that the initial ACE inhibitor, captopril, is quickly absorbed and eliminated. However, it is essential to understand that enalapril, along with most ACE inhibitors that came after it, is an inactive prodrug that necessitates hydrolysis to produce the active acid form, enalaprilat. [20]

Adverse effect:

- Dry cough.
- Too much potassium in the blood.
- dizziness
- Headaches.
- Loss of taste.
- Rarely, short-term worsening of kidney function.

b) Angiotensin receptor blockers
Angiotensin receptor blockers (ARBs) like losartan and telmisartan are powerful medications that effectively lower high blood pressure. These medications work by selectively blocking the AT1 receptor, which is responsible for the constriction of blood vessels. The binding of ARBs to the receptor can be either competitive or insurmountable. It is important to note that some ARBs are pro-drugs that

require conversion to an active metabolite to produce their therapeutic effect. Interestingly, ARBs can increase 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 AT2 receptors, which are responsible for vasodilation and anti-fibrotic effects, to enhance the therapeutic actions of ARBs. Overall, the primary therapeutic use for ARBs is as a powerful antihypertensive drug that effectively lowers high blood pressure. [18]

Examples:

1) Losartan

2) Candesartan

3) Valsartan

Pharmacokinetics

The oral bioavailability of ARBs varies and is dependent on the lipophilicity of the ARBs. The absorption of valsartan is limited when taken with food. Notably, all ARBs have a half-life of 6 to 24 hours, whereas other ARBs have limitations of 0.5 to 4 hours. Shows high levels of plasma protein binding (>95%). ARBs are excreted from the body in varying degrees as unchanged drugs and metabolites in the urine and feces. [21]

Adverse effect:

ARB administration is contraindicated in pregnant women due to its potential association with congenital anomalies. ARBs can cause a rapid decline in renal function in individuals suffering from renal hypoperfusion, such as renal artery stenosis, similar to ACE inhibitors. It is imperative to monitor GFR and serum K+ in CKD patients, especially those taking potassium-sparing diuretics. It is important to note that most ARBs are metabolized in the liver, and there are reports of liver dysfunction associated with their use. Lastly, it is essential to be aware that non-productive cough, the most common side effect of ACE inhibitors, is not a common occurrence with ARBs.[22]

c) Direct renin inhibitor

RAAS plays a crucial role in maintaining biological homeostasis by regulating blood volume and salt-water balance, thereby influencing blood pressure levels and tissue perfusion through various mechanisms.

Despite the critical function of the RAAS in maintaining homeostasis, prolonged activation of this system can result in renal damage and contribute to the advancement of chronic kidney disease. These alterations are influenced by various hemodynamic and nonhemodynamic effects of angiotensin II and aldosterone. Angiotensin II leads to increased intraglomerular pressure, which is recognized as an important factor in the progression of CKD. This increased pressure results mainly from a differential angiotensin II effect on afferent and efferent glomerular arterioles. [24]

Example:

1) Aliskiren

Pharmacokinetics

Aliskiren has a meager oral absorption rate of only 2.5% and its maximum plasma concentration is achieved within 1-3 hours of oral administration. After initiating once-daily oral administration of aliskiren, it takes around 5-8 days to reach a steady-state plasma concentration [25, 26]. In healthy volunteers, a single oral dose of 300mg of aliskiren has an elimination half-life of 40 hours. The elimination process is almost entirely via feces (91.5%), with 77.5% of the dose being excreted as the unchanged drug [27].

Adverse effect

According to the package insert, it is important to be aware of the primary adverse effect of Aliskiren which is diarrhea. It has been reported that approximately 2.3% of patients using this medication experience this side effect. Along with diarrhea, other adverse effects such as cough, rash, headaches, and dizziness have also been reported. Furthermore, clinical lab findings from clinical trials have shown that patients may experience increased blood urea nitrogen or serum creatinine, small decreases in hemoglobin and hematocrit, increases in serum potassium, elevated serum uric acid, and increased creatine kinase. It is important to note that serious adverse reactions such as fetal toxicity, anaphylactic reactions, head and neck angioedema, and hypotension have been reported in clinical trials.[28]

3) Sympathetic Inhibitors

The sympathetic nervous system plays a crucial role in regulating circulation and may be responsible for causing or maintaining clinical hypertension. Antihypertensive drugs primarily work by inhibiting the sympathetic pathways, with the most specific inhibitors being centrally acting agents and peripheral alpha-adrenergic blockers. Alpha-blockers, such as prazosin and terazosin, are highly effective in reducing blood pressure as monotherapy or in combination with other antihypertensive drugs.[29]

A) beta-adrenergic blocker

Example

1) Propranolol

2) Metoprolol

Pharmacokinetics

There are several ways to take beta-blockers: orally, intravenously, topically in the eyes, and intramuscularly. The range of dosages varies based on the particular drug. Metoprolol succinate, a longer-acting beta-blocker, is recommended once daily for outpatient usage. On the other hand, most beta-blockers are normally recommended twice daily. For instance, depending on the indication and dosage, propranolol, which has a half-life of roughly 4 hours, is typically prescribed up to 3 or 4 times per day. Therefore, to get the intended therapeutic effect, it is imperative that you strictly adhere to the recommended dosages.[31]

Adverse effect

The body is full of beta receptors, and using beta-blocker drugs to inhibit them can have several negative effects. Hypotension and bradycardia are frequent side effects. Additionally, patients may develop constipation, nausea, dizziness, fatigue, and sexual[31,32]

b) Alpha-adrenergic blocker

Alpha-blockers exert pharmacological effects by acting on the sympathetic nervous system. There are two types of alpha-adrenergic receptors: alpha 1 and alpha 2. Most alpha-1 adrenergic receptors are found in vascular smooth muscles of the skin, intestinal sphincter, kidneys, and brain. When triggered by catecholamines such as epinephrine and norepinephrine (NE), these receptors cause vasoconstriction, increasing blood pressure and peripheral resistance. Norepinephrine has a greater affinity for this receptor than adrenaline. Alpha-2 adrenergic receptors on peripheral nerve endings limit the release of norepinephrine upon stimulation. This process generates feedback to the NE, preventing its release. [33]

Example

1) prazosin

2) terazosin

Pharmacokinetics

When taken orally in a fasting state, tamsulosin and terazosin have a bioavailability of approximately 90%. Terazosin is typically 90-94% bound to plasma, and roughly 10-20% of it is excreted unchanged in urine and feces. The elimination half-life for terazosin is between 8-13 hours, with 40% eliminated through urine and 60% through feces. Dose adjustment is unnecessary for patients with renal impairment. However, patients with moderate hepatic impairment should receive titrated doses of terazosin with caution, as it's metabolized by the liver and excreted through the biliary tract.[34]

Adverse effect

harmful effects Non-selective alpha-blockers can cause various side effects, including hypotension, weakness, tachycardia, and tremor. These effects occur due to inhibition of alpha-1 receptors, which

causes vascular smooth muscles to relax and blood vessels to dilate. Additionally, antagonism of alpha-2 receptors causes the release of norepinephrine, which stimulates beta receptors and causes tremor and tachycardia. It is important to note that selective alpha-1 blockers are less likely to cause systemic effects such as tachycardia and tremor. However, due to vasodilation and relaxation of vascular smooth muscles, hypotension, syncope, dizziness, and headache may occur even with the first administration. [35]

4) Calcium channel blockers

These antagonists are divided into two major categories based on their primary physiological effects. Calcium channel antagonists efficiently inhibit calcium ion movement by interacting with "long-acting" L-type voltage-gated calcium channels in the heart, vascular smooth muscle, and pancreas. Non-dihydropyridines have depressant effects on the sinus (SA) and atrioventricular (AV) nodes, significantly slowing cardiac conduction and contraction. This allows effective treatment of hypertension, reduces oxygen requirements, and helps control the frequency of tachyarrhythmias. On the other hand, dihydropyridines have little direct effect on the myocardium at therapeutic doses and instead act as potent peripheral vasodilators. Because of this property, they are commonly used for hypertension, vasospasm after intracranial hemorrhage, and migraine.[36,37]

Example

1) Verapamil

2) nifedipine

Pharmacokinetics

Calcium channel antagonists are readily absorbed when taken orally but have low bioavailability due to hepatic first-pass metabolism by CYP3A4. These antagonists have high protein binding capacity and massive distribution. Repeated administration or overdose of these antagonists saturates the liver enzymes responsible for metabolism, thereby reducing the first-pass effect and increasing absorption of the active ingredient. Modified-release and metabolically saturated formulations may extend the half-life of various calcium channel antagonists. After metabolic side effects, renal excretion is the main elimination route for these antagonists.

Adverse effect

Non-dihydropyridines are known to cause constipation, worsened cardiac output, and bradycardia. Dihydropyridine can cause drowsiness, facial flushing, headache, and peripheral edema. It should be noted that this peripheral edema is caused by the redistribution of fluid from the intravascular space to the interstitium. Additionally, there are numerous reports of gingival hyperplasia associated with these drugs. [38]

5) Vasodilators

Vasodilators are highly effective drugs used in the treatment of various diseases, especially systemic hypertension. Additionally, it is suitable for treating myocardial infarction, angina pectoris, heart failure, stroke, chronic kidney disease, and pre-eclampsia. These drugs dilate blood vessels, prevent them from narrowing, and increase blood flow to various organs in the body. Vasodilators bind to receptors on the endothelium of blood vessels. These receptors stimulate the release of calcium and activate the enzyme nitric oxide synthase. NO synthase then converts L-arginine to nitric oxide (NO), which diffuses from the endothelial cells and enters vascular smooth muscle cells. NO activates GTP, converting it to cGMP, which in turn stimulates myosin light chain phosphatase. This enzyme removes single phosphates from myosin and actin filaments, causing relaxation of vascular smooth muscle. [39, 40]

Example

1) Hydralazine

2) nitroprusside sod.

Pharmacokinetics

Indeed, direct vasodilators, while effective in managing hypertension, are typically not the initial choice in antihypertensive therapy due to certain characteristics. The drugs in this class possess a relatively short half-life, necessitating multiple doses throughout the day to maintain their therapeutic effect. Furthermore, they are predominantly metabolized by the liver and eliminated from the body through renal excretion. These pharmacokinetic properties contribute to the need for close monitoring and potential dose adjustments to achieve optimal blood pressure control. [41]

Adverse effect

Some of these side effects may require treatment with other medicines. Side effects may include Fast heartbeat (heart palpitations) Fluid build-up in the body (endotracheal edema) nausea vomiting headache excessive hair growth joint pain chest pain [8].

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