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Review Article

Studies On Various Classification Of Antihypertensive Drugs

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ABSTRACT

Many antihypertensive medication classes are available, making successful treatment of hypertension with minimal side effects possible. Both their mechanisms of action and adverse effects are the two main topics covered in this review of the various pharmacological classes of antihypertensive medications. A pharmacological approach is used to analyze the mechanism of action, including the extra-arterial sites of action, the different sites along the arterial system, and the molecular receptor targets. This helps to clarify which type of hypertension a particular pharmacological class of antihypertensive drug is most indicated. Additionally, in order to better understand side effects and which patient medications are contraindicated; side effects are discussed and explained through their pharmacological causes. Since these topics are covered in other papers in this issue, this review does not evaluate the efficacy of combination therapies or monotherapies in large-scale randomized clinical trials. This article describes the five main pharmacological classes of hypertension medications: calcium channel blockers, angiotensin II receptor antagonists, angiotensin converting enzyme inhibitors, and beta-blockers. A more succinct description is given for four more pharmacological classes: direct acting vasodilators, renin inhibitors, alpha adrenergic receptor blockers, and centrally acting drugs.

INTRODUCTION

Many antihypertensive medication classes are available, making successful treatment of hypertension with minimal side effects possible. Beginning with medications discovered 60 years ago, such as thiazide diuretics (1958), and ending with the newest antihypertensive agent on the market, the orally active direct renin-inhibitor aleskiren, which was discovered more than ten years ago (2000), pharmacological research has been applied to the treatment of hypertension continuously [1]. In between, there has been a continuous rate of discovery, including spironolactone (1957), beta-blockers (propranolol, 1973), centrally acting alpha-2 adrenergic receptor agonists (coniine, 1970s), alpha1- adrenergic

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receptor blocker (prazosin, 1975), angiotensin converting enzyme inhibitors (captopril, 1977), calcium channel blockers (verapamil, 1977), and angiotensin II receptor blockers (losartan, 1993) [1]. This review's main objective is to provide an overview of the several pharmacological groups of antihypertensive medications by focusing on two key areas: their modes of action and adverse effects. To better understand which type of hypertension a given pharmacological class of antihypertensive drug is most indicated for, the mechanism of action is analyzed using a pharmacological approach, and i.e. the molecular receptor targets, the various sites along the arterial system, and the extra-arterial sites of action (see other articles of this issue). .. Furthermore, the pharmacological mechanisms underlying side effects are elucidated to gain a deeper understanding of their mechanism of action and the patients for whom certain drugs are contraindicated. Since these topics are covered in other papers in this issue, this review does not evaluate the efficacy of combination therapies or monotherapies in large-scale randomized clinical trials. This article describes the five main pharmacological groups of hypertension medications: calcium channel blockers, angiotensin converting enzyme inhibitors, beta blockers, and angiotensin II receptor antagonists. Shorter descriptions are given to four more pharmacological classes: direct acting vasodilators, renin inhibitors, alpha-adrenergic receptor blockers, and centrally acting drugs.

MECHANISM OF ACTION

BETA-BLOCKERS

The pharmacodynamic characteristics of beta-blockers, a varied family of pharmaceuticals, are determined by their partial agonist activity, cardiac selectivity, and related vasodilating effects. By varying in the degree of cardiac output decrease and vasodilatation, they all lower blood pressure to the same degree based on their pharmacological characteristics [2].

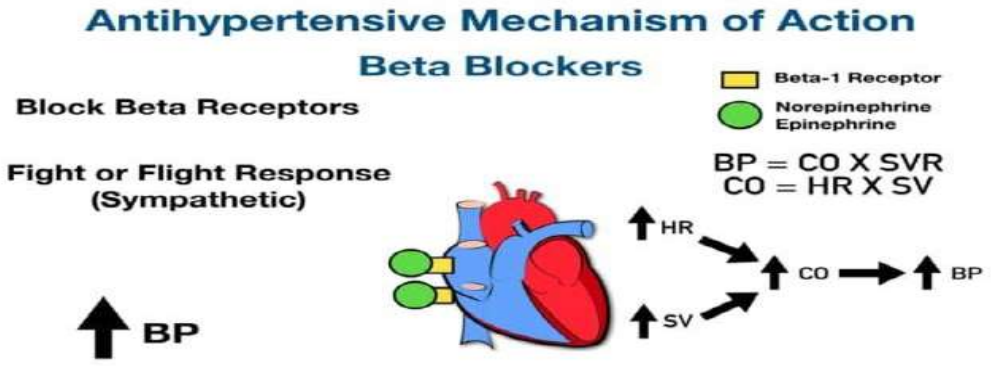

Figure 1.The antihypertensive effect of beta-blockers has been explained by a number of mechanisms of action. One of the main ones is the reduction in cardiac output that occurs in reaction to bradycardia, which lowers mean blood pressure. It is not surprising that there is an increase in total peripheral resistance when blood pressure is lowered because this stimulates the baroreflex system. Nevertheless, the baroreceptors' reset reduced this increment. It is also possible that there will be a decrease in sympathetic activity of central origin, which will lower vasomotor tone and could be linked to or separate from a decrease in rennin secretion [3] It has also been proposed that an impact on pre-junctional beta-receptors reduces the release of norepinephrine. Depending on the properties of the beta-blocker, there are varying degrees of association between the

aforementioned modes of action. After beta1 selective blockers (bisoprolol, atenolol) work preferentially on the cardiac beta1-adrenergic receptor, non-opposed beta2 arteriolar vasodilatation may also help decrease blood pressure. Compared to non-vasodilating beta-blockers (atenolol, metoprolol), the lowering of blood pressure following vasodilating beta-blockers is accompanied by a lesser decrease in heart rate and a lesser increase in total peripheral resistance. Beta2-adrenergic receptor sites (celiprolol, nebivolol), alpha1-adrenergic receptor sites (carvedilol, labetalol), and NO potentiating receptor sites (nebivolol) are frequently the sites of partial agonist activity for vasodilating beta-blocker. Their vasodilating action on small arteries is linked to a decrease in arterial stiffness, which is lessened in comparison to non-vasodilating beta-blockers, and is not entirely explained by the merely lowering of blood pressure (less distension of the stiff parts of the large artery wall). Therefore, the different aspects of central and peripheral hemodynamics that vasodilating beta-blocker affect include heart rate and cardiac output reduction, large artery relaxation, and small artery vasodilatation. Nevertheless, through a number of pathways, non-vasodilating beta-blockers such atenolol can have neutral or harmful effects on the vascular system [4]. For example, despite catecholamine's having less harmful effects on the heart than beta-blockers, atenolol does not reduce total peripheral resistance or sympathetic drive. In hypertensive patients, atenolol reduces target organ damage less than renin-angiotensin system blockers. As a result, after beta-blockers, there is still some vasoconstriction, an increased media-to-lumen ratio, left ventricular hypertrophy, and carotid intimamedia thickness [5]. Even when atenolol is combined with a calcium-channel blocker [6], the reduction in aortic stiffness and central blood pressure is less than that of vasodilators [7]. When the blood pressure is not lowered sufficiently to release the stiff components of the arterial wall, nonvasodilating beta-blockers might even directly have a "pro-fibrotic" impact that stiffens big arteries [8]. Beta-blockers' harmful effects may result from a number of processes, including enhanced TGF-α production and the cross-linking of collagen and elating fibers. When beta2-or alpha-adrenergic receptors are activated, the latter happens. Another method is the activation of lysyl-oxidase. Lastly, the side effects of beta-blockers, such as insulin resistance and an elevated risk of incident diabetes, can exacerbate arterial damage [9].

Side effects

Because beta-2 receptors are necessary for adrenaline bronchodilatation, patients with moderate to severe asthma, unstable heart failure due to systolic dysfunction, second- or third-degree atrioventricular block, or sick sinus syndrome (without a pacemaker) shouldn't take beta-blockers. Beta-blockers may exacerbate glucose intolerance and conceal the signs of hypoglycemia. [10] Bright dreams, sleeplessness, delusions, and melancholy can all arise during beta-blocker therapy; these side effects are more common with the highly lipid-soluble beta-blockers (propranolol, metoprolol, and pindolol), which may have a greater ability to enter the central nervous system. A typical side effect of several beta-blockers is impotence, though it may be less likely with vasodilating beta-blockers.

Loop diuretics

The two loop diuretics that are most commonly used are furosemide and bumetanide.

Mechanisms of action

The thick ascending limb of the loop of Hanley is where the apical membrane of the nephron is where loop diuretics act. They prevent the reabsorption of Na+ and chloride (Cl-) at the Na+/K+ /2Clcotransporter (NKCC), through rivalry with Cl-.A sigmoid curve represents the typical dose-response relationship, or the link

between Na+ excretion and loop diuretic excretion rate. When NSAIDs are present, it can be moved to the right and downward, which will block the formation of prostaglandins [11]. Because of increased K+ and H+ excretion in the collecting tubule in reaction to the higher Na+ concentration at this level and considerable secondary hyperaldosteronism in response to hypovolemia, Na+ excretion is linked to hypokalemia and mild metabolic alkalosis. [12] A decrease in free water excretion during water loading and reabsorption during dehydration due to a decreased osmotic gradient in the medulla are two other significant effects of loop diuretics. When the paracellular Ca2+ transport across renal epithelia is inhibited, an increase in Ca2+ excretion is also seen [2]. The extracellular fluid volume is decreased by loop diuretics, lowering blood pressure. Lowering cardiac output and venous return are caused by the decrease in plasma volume that follows an increase in Na+ excretion. The sympathetic nervous system and the renin-angiotensin-aldosterone system may be stimulated by these variations in plasma volume. Furosemide causes diuresis that starts quickly—within an hour—peaks between three and six hours later, and then starts to lessen after twelve hours [1].

Side effects

Hyponatremia (depletion and dilution of Na+), hypokalemia, metabolic alkalosis, hypovolemia, hypotension, and, to a lesser degree, hyperuricemia, hypocalcaemia, hypomagnesaemia, hyperglycemia, hyperlipidemia, urinary urgency, and impotence are dose-dependent side effects of loop diuretics [12]. For gout sufferers, loop diuretics are contraindicated.

Thiazide

Among the most widely used thiazide diuretics are hydrochlorothiazide, chlortalidone, and indapamide.

Mechanisms of action

Inhibiting the coupled reabsorption of Na+ and Cl-, thiazide diuretics act on the nephron at the apical membrane in the early convoluted distal tubule. When compared to the more proximal site of action of loop diuretics (the ascending limb of the loop of Henley), the thiazide's natriuretic effect is less than that of loop diuretics because a smaller fraction of the filtered load of Na+ is reabsorbed at the distal tubular site of action [13]. Due to both a substantial secondary hyperaldosteronism in response to hypovolemia and an increased K+ and H+ excretion in the collecting tubule in response to the higher Na+ concentration at this level, Na+ excretion is linked to hypokalemia and mild metabolic alkalosis. The ability to dilute urine is compromised by thiazide diuretics. By contrast to loop diuretics, thiazide diuretics preserve urinary concentrating mechanisms [11]. Like loop diuretics, thiazide diuretics lower blood pressure by decreasing the volume of extracellular fluid [14]. In the context of a diet without salt added, the early response to thiazide diuretics causes a net Na+ loss of 100 to 300 mol in a few days, which equates to a 1 to 2 L reduction in extracellular fluid volume. Na+ concentrations in plasma remain constant throughout the process. Venous return is decreased and cardiac output is decreased as a result of the decrease in plasma volume brought on by an increase in Na+ excretion. The renin-angiotensin-aldosterone system and the sympathetic nervous system may be activated by these variations in plasma volume. When using hydrochlorothiazide, diuresis starts quickly—within two hours, peaking between three and six hours, and having less of an impact after twelve hours. When a longer duration of natriuresis is required, chlortalidone, a longer-acting thiazide, may be helpful [14].

Side effects

Hyponatremia (Na+ depletion and dilution), hypokalemia, metabolic alkalosis, hypovolemia, hypotension, and, to a lesser degree,

hyperuricemia, hypomagnesaemia, hyperglycemia, hyperlipidemia, and impotence are dose-dependent side effects of thiazide diuretics. They bear resemblance to loop diuretic ones [12]. The sole deviation is that hypocalcaemia happens following thiazide diuretics rather than hypocalcaemia following loop diuretics. In fact, following thiazide diuretics, there is an increase in Ca2+ reabsorption at the distal tubule level [15]. Lowering the Na+ concentration at the level of tubule epithelial cells is the mechanism. Indeed, thiazides increase the driving force for reabsorption from the lumen by indirectly increasing the basolateral Na+/Ca2+ antiproton activity, which in turn lowers the intracellular Ca2+ concentration. Thiazide diuretics are contra-indicated in patients with gout.

Potassium-sparing diuretic

This subclass contains medications that function independently of aldosterone, such as amiloride and triamterene, as well as competitive antagonists of aldosterone, such as spironolactone and eplerenone.

Mechanisms of action

These medications prevent active Na+ absorption at the collecting duct and late distal tubule levels. Specifically, spironolactone functions as a competitive antagonist of mineral corticoid receptors, which are found in the tubular cells' cytoplasm in the collecting duct and late distal tubule. Spironolactone prevents its legend aldosterone from binding, which prevents aldosterone from moving to the nucleus of cells, homodimerizing, and attaching to hormone response elements found in the promoter of some genes. The inactivation of Na+ absorption is caused by this blockade, which lowers the levels of proteins that control ionic and water transports, primarily the glucocorticoid-induced kinase (SGK1), the Na+/K+ pump, and the epithelial sodium channel (ENaC). On the other hand, independently of aldosterone, amiloride and triamterene block ENaC in the collecting duct's luminal membrane [16]. Since a smaller portion of the filtered load of Na+ is reabsorbed at this distal site of action than at the more proximal site of action of loop diuretics and thiazide diuretics, only a modest natriuretic effect can be anticipated.

Side effect

A common side effect is hyperkalemia, which is more common in patients taking an ACEI, an ARB, or an NSAID, receiving potassium-sparing diuretics, diabetes, heart failure, or chronic renal disease. There is a link between metabolic acidosis and hyperkalemia. Bilateral gynecomastia, impotence, decreased libido, and mastodynia are common side effects of spironolactone therapy. Since spironolactone prevents dihydrotestosterone from binding to androgen receptors, increasing the clearance of testosterone, they are connected to the sexual side effects of the drug. These sexual side effects significantly lessen the complexity of treatments with amiloride, triamterene, or eplerenone, a more selective aldosterone antagonist [16]. Potassium-sparing diuretics are contraindicated in patients with acute or severe renal failure (eGFR < 30 mL/min), especially mineral corticoid receptor antagonists.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Captopril was the first ACEI to be made available for the treatment of hypertension in the early 1980s. Enalapril, perindopril, lisinopril, ramipril, quinapril, benazepril, cilazapril, trasdolapril, fosinopril, moexipril, imidapril, and zofenopril swiftly followed.

Mechanisms of action

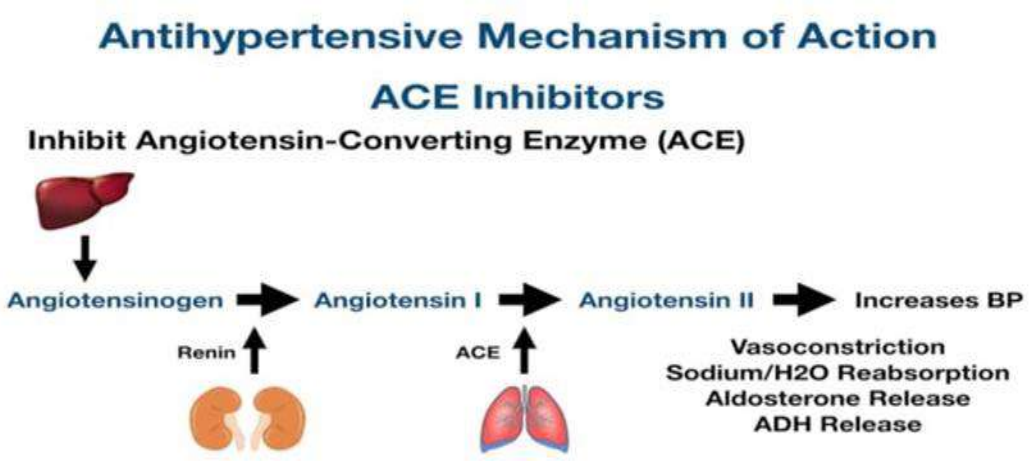

Figure 2.The pluripotent zinc metalloproteinase known as angiotensin converting enzyme (ACE) is the target of angiotensin converting enzyme inhibitors (ACEIs), which catalyze the conversion of angiotensin I to angiotensin II. [17] ACE is found in pulmonary endothelial cells as well as in the endothelial cells of capillaries, venules, and small and large vessels. Crucially, because of its strategic location within the lungs and the lungs' strategic location in the general circulation, ACE may regulate the amount of angiotensin II that enters the systemic arterial circulation. The binding affinity of ACEIs for tissue ACE is a crucial characteristic that is influenced by their tissue binding affinity, potency, lipophilicity, and tissue retention. Both tissue retention and inhibitor binding affinity can help to extend the inhibition of ACE, even though tissue retention is not necessary when ACEI concentrations are high, such as during the first half of the 24-hour period. Strong vasodilators are ACEIs [12]. ACEIs are unable to inhibit the production of angiotensin II by other tissue-based proteases, such as chymase [18], which can eventually unregulate, especially in the heart and vasculature [18], and lessen the ACEIs' ability to lower blood pressure. As a result, ACEIs may raise the plasma concentration of angiotensin (1–7), an agent that acts as a vasodilator and antiproliferative and is formed in the endothelium layer of human blood vessels [19].

Side effects

ACEIs are typically well tolerated medications. But when prescribing these medications, one should be aware of the risk of cough and angioedema. Cough is widespread (10–20%). Class plays a role in this. The reason behind it is attributed to a rise in bradykinin levels and potentially an increase in the concentration of other peptides like substance P. The characteristic of an ACEI-induced cough is that it is dry, uncomfortable, and unproductive. One potentially fatal side effect is angioneurotic edema. Similar to cough, it can be attributed to elevated bradykinin concentrations as well as potentially elevated levels of other peptides like substance P. The Octave study [20] reports that this is an uncommon side effect that affects 0.55% of white patients and 1.62% of black patients. The suppression of erythropoietin production in response to the accumulation of N-acetyl-serylaspartyl-Lysol-praline in plasma, a strong natural inhibitor of hematopoietic stem cell proliferation, is most likely the cause of ACEI-related anemia [21].

ANGIOTENSIN II RECEPTOR BLOCKERS

Losartan was the first angiotensin II receptor blocker (ARB) to be made accessible for the treatment of hypertension in the late 1990s.

Candesartan, eprosartan, irbesartan, valsartan, telmisartan, and olmesartan quickly followed.

Mechanisms of action

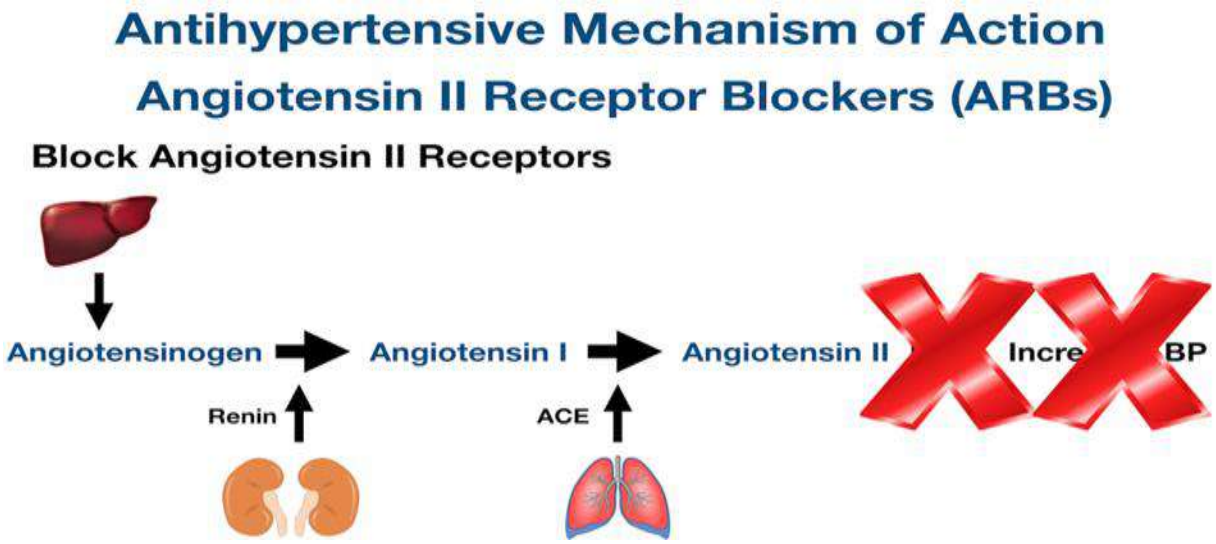

Figure 3. At the level of the angiotensin II type 1 subtype receptor (AT1), ARBs counteract the effects of angiotensin II. The AT1 receptor, which is present in high concentration in a number of organs, including smooth muscle cells, the heart, kidney, and aorta, is highly affinity for all ARBs. Because of their competitive binding and sluggish dissociation from the AT1 receptor, ARBs used in clinical practice can reduce blood pressure for longer periods of time than indicated by their pharmacokinetic properties. "Sartans" is another term for ARBs. Cell expansion, proliferation, and contraction are caused by angiotensin II's activation of AT1 receptors. This phenomenon is not limited to the location of small artery vascular smooth muscle cells (VSMCs), which is the primary effect of ARBs, but also includes the site of large artery VSMC, cardiac myocytes, and fibroblasts.

Side effects

In general, ARBs are well-tolerated medications. Since ARBs don't affect kininase II or other enzymes involved in the metabolism of substance P or other peptides, they are considerably less likely to cause cough and angioedema than ACEIs. Due to similar processes, functional renal insufficiency is just as common as ACEIs. ARBs and ACEIs are contraindicated in the second and third trimesters of pregnancy for similar reasons. Hyperkalemia is rare, unless the patient is getting potassium-sparing diuretics or potassium supplements, and they have heart failure, diabetes, or chronic renal disease.

CALCIUM-CHANNEL BLOCKERS

Dihydropyridines (DHPs), such as nifedipine [22] and amlodipine [23], and verapamil (a benzodiazepine) are examples of the diverse class of medications known as calcium-channel blockers (CCBs).

Mechanism of action

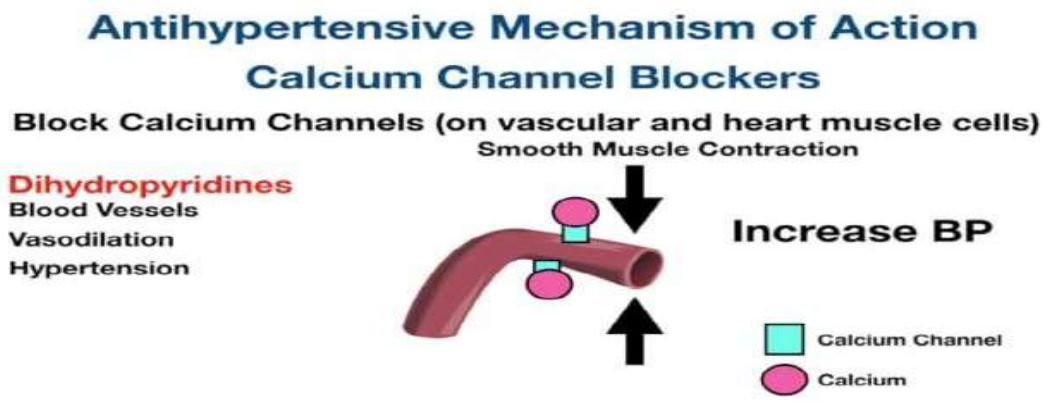

Figure 4.The voltage-dependent L-type calcium channels are blocked by DHPs [24]. The letter "L" stands for long-lasting, alluding to the duration of activation. DHPs thereby prevent the depolarization of cardiac myocytes, vascular smooth muscle cells (VSMCs), and cardiac nodal tissue (atrioventricular and senatorial nodes), all of which are mainly dependent on Ca2+ influx. Vascular selectivity is possessed by DHP. In contrast, verapamil and diltiazem exhibit cardiac selectivity, meaning they work better in cardiac muscle than in VSMCs. They block the calcium channel of the VSMC more so than the cardiac myocyte's [23]. The reason behind the vascular selectivity of DHPs has been attributed to the depolarized resting potential of VSMCs, which is higher in the "high affinity" inactivated state of the L-type calcium channel compared to cardiac myocytes [25]. Verapamil and diltiazem's use-dependency, or their greater blocking of the L-type calcium channel with repeated depolarization, has been used to explain their cardiac selectivity [25].

Side effects

In general, CCBs are well-tolerated medications. Ankle edema, headaches, flushing, and tachycardia are frequently brought on by high dosages of DHPs; their mechanisms of action have already been discussed [26]. Verapamil overdoses may result in constipation. Following any CCB, gingival hypertrophy can be seen.

CONCLUSION

In summary, the different ways in which the pharmacological classes of antihypertensive medications discussed in this review work demonstrate their complementary roles in managing hypertension, which is widely recognized as a mosaic of path physiological abnormalities. It is feasible to treat hypertension effectively and with little adverse effects. An improved understanding of the molecular receptor targets, the different sites of action along the arterial system, and the extra arterial sites of action enables the doctor to determine which patients' medications are contraindicated and for which type of hypertension a particular pharmacological class of antihypertensive drug is most appropriate. As a result of the former, ideal qualities should also have a fast-acting, high blood pressure-lowering effect as monotherapy, a continuous efficacy for 24 hours following a once-daily dose, a distinct dose-response relationship that facilitates simple drug dosage monitoring, and an ideal tolerability profile.

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