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A REVIEW ON SOME SELECTED ANTIHYPERTENSIVE AGENTS

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ABSTRACT

Hypertension is one of the major public health challenges worldwide. Angiotensin receptor blockers and calcium channel blockers are among the first line antihypertensive drugs. The aim of study is to estimate the reaction of the telmisartan-amlodipine combination at distinctive doses of on hypertension. The combination of drugs with different mechanism of action has become an alternative to improve low blood pressure and control enhance adherence to the treatment and reduce adverse events.

Key words:

Hypertension, telmisartan, amlodipine, monotherapy, combination therapy.

1.INTRODUCTION

Hypertension is defined conventionally as blood pressure (BP) 140/90. Hypertension is called 'the silent killer', because it usually has no symptoms. hypertension is linked with the sclerosis of the avenue, is called as atherosclerotic, and is a factor in 75% of all strokes and heart attacks. The body controls circulatory strain by a among baroreceptors and effector nerves, essentially adrenergic in nature. This framework is balanced by a peptide framework (angiotensin/renin)(1). Antihypertensive medications perplexing criticism mechanisms are perpetually utilized in the treatment of hypertension albeit a couple among them, for example, ganglion obstructing drugs, do track down their dispersed application in an assortment of other helpful, symptomatic and surgery(2). Many chance factors are worried within the improvement of the disease. Hypertension represents a modifiable hazard factor for coronary artery disorder(3). Hypertension is a result of numerous infection. Hemodynamically, pulse is an element of how much blood siphoned by the heart and the straight forwardness with which the blood course through the fringe vasculature. Essential hypertension is the most widely recognized type of hypertension, albeit advance have been made in the distinguishing proof and control of essential hypertension, the etiology of these type of hypertension has not yet been settled. Renal hypertension can be made by tentatively causing renal vein stenosis in creatures.

Renal artery stenosis also may occur in pathological conditions of the kidney, such as nephritis , renal artery thrombosis, renal artery infection, or other condition that restrict blood flow through the renal artery. Hypertension likewise may begin from neurotic states in the CNS like malignancies. The potential of antihypertensive (AH) marketers, which includes diuretics, b-blockers, angiotensin changing enzyme inhibitors, calcium channel blockers and angiotensin receptor blockers, to reduce CVD mortality and morbidity is nicely hooked up(4).

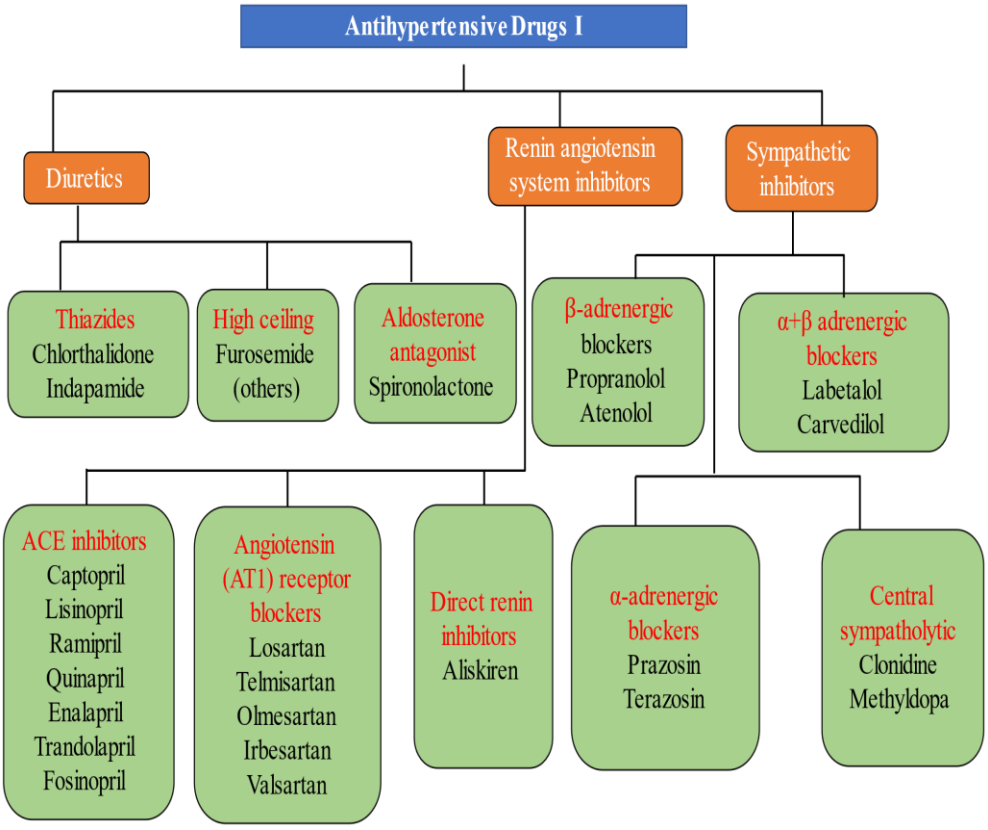
1.1 **Hypertensive heart disease**:

Hypertensive heart disease or hypertensive cardiomyopathy is the disorder of the heart because of systemic hypertension of prolonged duration and manifesting by using left ventricular hypertrophy. Even mild hypertension (blood pressure more than 140/90 mmHg) of enough period may additionally set off hypertensive coronary heart sickness. It is second most commonplace form of heart disease after IHD. As already mentioned, high blood pressure predisposes to atherosclerosis(5).

1.2 Antihypertensive Drug:

Antihypertensives drugs are a class of medicine or drugs that are used to treatment of hypertension (high blood pressure). Antihypertensive drug therapy has been remarkably improved in the last 60 years. Different classes of drugs have received prominence with passage of time in this period before 1950 hardly any effective and tolerated antihypertensive was available(6).

2. CLASSIFICATION



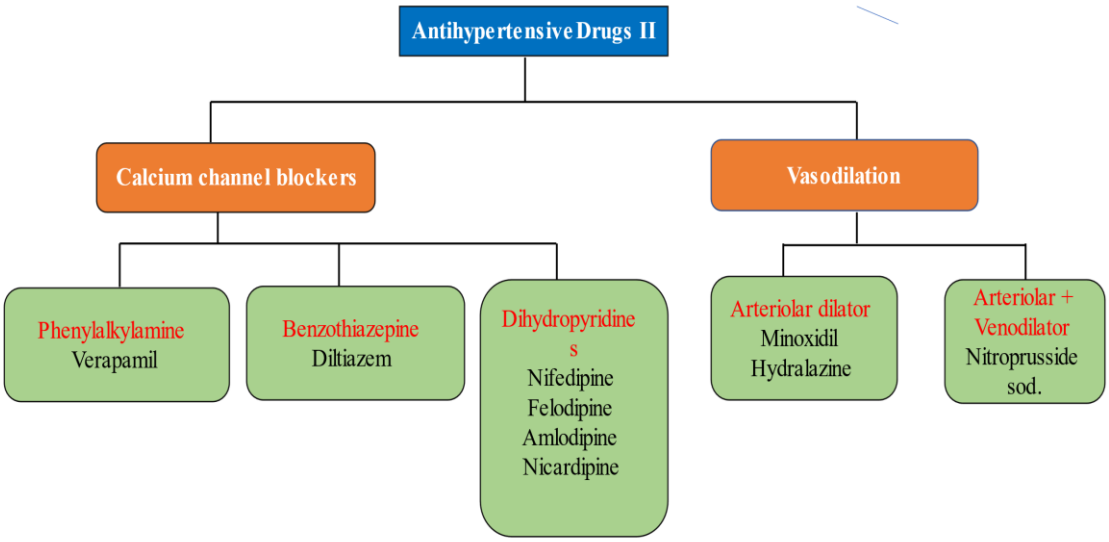


Figure 1 Classification of antihypertensive agents

3. PHARMACOTHERAPY

Drug therapy is suggested for individuals with blood pressure ≥a hundred and forty/ninety mmHg. Choice of antihypertensive dealers and their combinations should rely on age, severity of hypertension, cardiovascular hazard factors, comorbid conditions, cost, facet consequences and frequency of dosing. The antihypertensive capsules encompass α-blockers, β-blockers, CCBs (calcium channel blockers)(7).

3.1 single drug therapy:

All ARBs commercially available in the America except azilsartan were to begin with accepted by way of the Food and Drug Administration (FDA) for the treatment of hypertension. More research have validated dose belong to low blood pressure even though the dose response is particularly shallow as compared with that of a few other antihypertensive drugs consisting of CCBs. Subsequent studies have established that pills in this category are also adequate when given as single sellers in treating each systolic hypertension and diastolic hypertension, remoted systolic high blood pressure, and hypertensive sufferers who're elderly or have diabetes and/or the metabolic syndrome(8).

3.2 RAAS System:

The RAAS system originates from renin synthesis. Reduced cardiac output reduces renal blood float and turns on the RAAS machine. The renin–angiotensin system has been implicated in high blood pressure-related cardiometabolic syndrome, because accelerated concentrations of circulating angiotensinogen, renin and angiotensin-converting enzyme action have been notified in individuals characterized as dysmetabolic patients(9). Renin is synthesized within the kidneys as an inactive shape and launched into stream in reaction to low step of intratubular sodium, low blood pressure within the interlobular artery of renal Malpighian tuft, and supportive actuate. In the blood circulation pro-renin is start with the aid of proteolytic and non proteolytic mechanisms to supply the active shape. now the start renin catalyses the schism of the

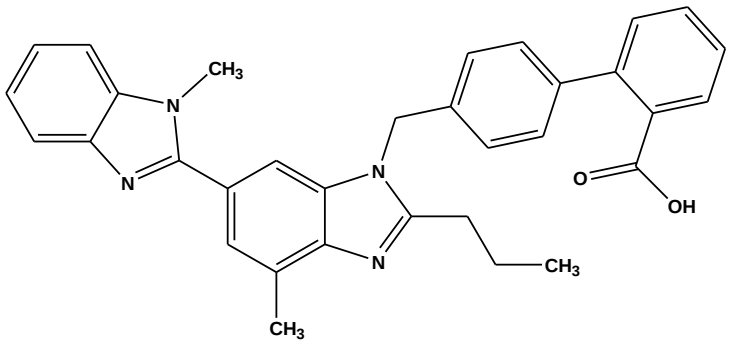
glycoprotein angiotensinogen, producing angiotensin I. angiotensin I is break through the angiotensin-changing enzyme to provide angiotensin II, the main repressor in the renin angiotensin aldosterone system, while neutral endopeptidases break angiotensin I to supply angiotensin-(1-7), some other lively peptide of this device that normally against the consequence of angiotensin II. Most of the acknowledged swarming and profibrotic effects of angiotensin II are via the angiotensin kind 1 receptor, however it can also bind to the angiotensin II kind 2 receptor thereby activate contrary consequences to the ones on the angiotensin I receptor. Angiotensin-(1-7) can also be generate by means of the breakage of angiotensin II via angiotensin-converting enzyme 2, as a result reducing the attention in want of Ang II, which promotes vasoconstriction on coronary and vascular tissues. Aldosterone is some other effecter molecule of the renin angiotensin aldosterone system, whose synthesis and excretion are inspired by using angiotensin II thru the angiotensin I receptor within the adrenal cortex. Through unique activity on the distal uriniferous tubule of the kidney, aldosterone encourage sodium metabolism, water detention, and potassium and magnesium loss, thereby regulating extracellular area capacity and blood pressure(10).

4. SINGLE DRUG PROFILE:

4.1 Telmisartan:

It works through blocking a substance within the body that reasons blood vessels to narrow. while a end result, it relaxes blood vessels. This lowers blood strain and increases the deliver of vital fluid and oxygen to the coronary heart(11). Telmisartan is an ARB that well-known shows a strong and sustained antihypertensive impact over 24 h and is secreted into the bile(12). Telmisartan was approved by the united states Food and Drug Administration in November 1998 and by the European Commission in December 1998 for the treatment of hypertension. Telmisartan is an angiotensin II receptor blocker, shows excessive affinity for the angiotensin II, kind I (AT-I) receptors, has an extended period of action and has longest half of-life of any ARB(13). Telmisartan is a extraordinarily selective ARB for the AT1 receptor and, because the withdrawal of this agent is ~24 h, one time in a day administration of telmisartan is resulted to decrease blood strain (BP) for an entire 24 h(14). Is a broadly prescribed anti-hypertensive drugs(15).

Structure:



Iupac:

names 2-(4-{[4-methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl] methyl}phenyl)benzoic acid(16).

Class:

Renin angiotensin system inhibitors

Subclass:

Angiotensin receptor blockers

Chemistry:

Telmisartan (BIBR 277) is chemically expressed as [1,1'-biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-(CAS). It is a white translucent powder with a molecular weight of 514.6 and a melting point of 261 to 263°C (47). The solubility of telmisartan in the range of pH 3–9 it is only poorly soluble. Telmisartan is active as such: it is not a prodrug. The telmisartan molecule is unusually stable. No Phase I-type metabolism has been observed. Among the AII antagonists, telmisartan is the most lipophilic compound with a partition coefficient log P = 3.2 (n-octanol buffer at pH 7.4). Due to its physicochemical characteristics, telmisartan display excellent oral absorption and tissue penetration aqueous solutions is strongly pH-dependent, with maximum solubility observed at high and low pH(17).

Mode Of Action:

Telmisartan continues blood vessels from narrowing, which hypotension and improves blood float(18). The near dating among the RAAS device and hypertension has led to compelling indicators to block the formation or pastime of angiotensin II via use of angiotensin changing agitator prohibit and angiotensin II receptor hinder. illustrates the current biochemical pathways involved inside the production of angiotensin. In the RAAS system, the inactive prorenin is proteolytically converted to enzymatically lively renin in response to renal baroreceptor signalling, sodium concentration modifications, sympathetic nerve stimulation and poor comments through Ang II on juxtaglomerular cells. Angiotensinogen, an a2-globulin produced mainly inside the liver, is cleaved through renin to generate angiotensin 1 (Ang I; Ang (1--10)). In the medical institution, a count of the rate of Ang I manufacturing is supplied via plasma renin activity (PRA). Angiotensin II produces its 'terrible' biological consequences via binding the Ang II--AT1-R within the heart, vasculature, kidneys, adrenal glands, brain and adipocytes. Formation of the Ang II--AT1-R complicated outcomes in the poor-comments inhibition of renin launch and thee manufacturing and free of aldosterone from the adrenal cortex. By contrast, the interplay of Ang II with the Ang II kind 2 receptor (AT2-R), that's present generally simplest in low concentrations in adults, produces typically 'fantastic' outcomes each inside the manage of vital pressure and inside the discount and prevention of organ harm, thru receptor-mediated vasodilatation, nitric-oxide (NO) release, kinin-mediated antiproliferative and proapoptotic effects inside the coronary heart and vasculature, and beneficial effects on sodium resorption by means of the proximal tubules within the kidney(19).

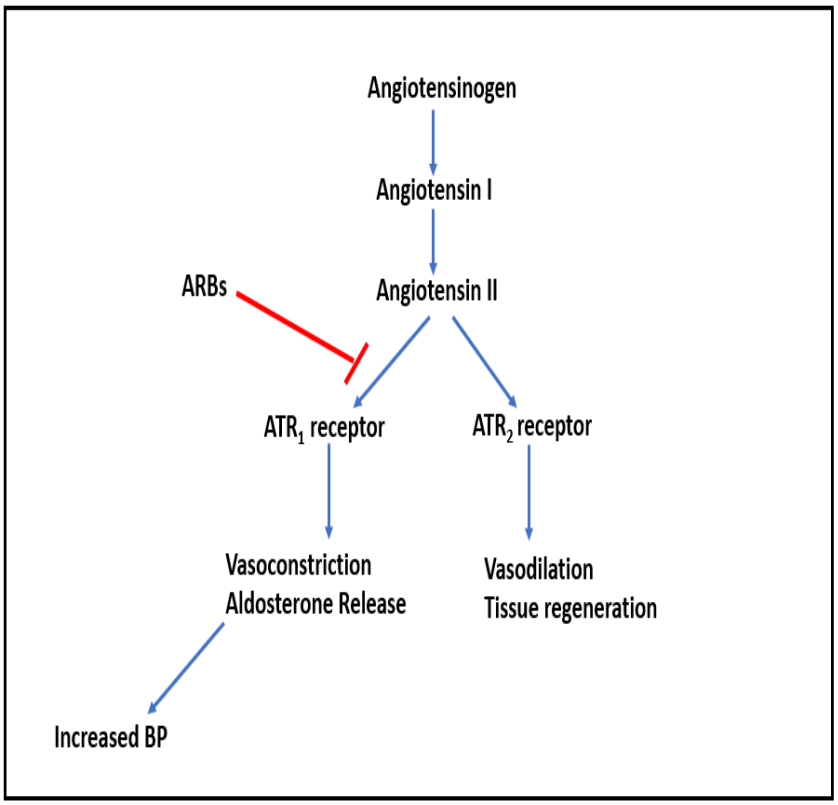


Figure 2 MOA of telmisartan

Pharmacodynamics

Telmisartan is highly specific for the AT1 receptor (Ki = 3.7 ± 0.7 nm.) and has very little affinity for the AT2 receptor (Ki = >10,000 nm.), or for other neurohormonal receptor

structures, along with acetylcholine, catecholamine, dopamine, histamine, serotonin or imipramine receptors. Thus, telmisartan does no longer block the motion of different receptor structures involved in CV characteristic. Telmisartan binds to the AT1 receptor with the most powerful affinity of all available ARBs(20).

Pharmacokinetics:

Alongside interactions with the receptor, pharmacokinetic residences are essential elements that have an impact on the pharmacodynamics of a drug. Telmisartan is the more lipophilic of all angiotensin receptor blockers, with a partition coefficient of log three.2 (n-octanol/buffer at pH 7.4). The excessive lipophilicity of telmisartan facilitates oral absorption and lets in tissue and cell penetration. Moreover, this physicochemical assets effects in its high extent of distribution of about 500 l (7 l/kg). In assessment, candesartan, valsartan, eprosartan and the active metabolite of losartan have smaller volumes of distribution (0.13 – 0.24 l/kg) than telmisartan.

Telmisartan:

T max (h) : 1

Bioavailability : 43

t½ (h) : 24

V d (I) : 500

Interaction with food : No

Elimination in faeces/urine (%) : Greater than 98% faecal(21).

Pharmacology of telmisartan:

Currently, there are seven ARBs that are commercially accessible, with telmisartan presenting distinct pharmacologic properties compared to other agents in its class. Among commercially available ARBs, telmisartan has the highest binding affinity for the AT1 receptor and exhibits unbreakable but reversible binding to this receptor. Telmisartan is also very lipophilic, which makes it easier for tissues to absorb it via the mouth. cell penetration, as evidenced by its substantial volume of distribution of around 500 L, hence inhibiting both local and systemic RAS. More than 90% of telmisartan is excreted in the faeces, in contrast to other ARBs, which are excreted to variable degrees via the kidneys. The lengthy terminal elimination half-life of telmisartan, which is approximately 24 hours, is a crucial distinguishing factor and suggests a protracted duration of activity(22).

Solubility:

soluble in Dichloromethane Solubility of Telmisartan is Practically indissoluble in water, moderately soluble in Methanol and Ethanol, sparingly(23).

Metabolic outcomes of telmisartan:

Vascular risk factors of hypertension, hyperglycaemia, and atherogenic dyslipidemia are established abnormalities in subjects with kind 2 diabetes. Diabetes will increase cardiovascular risk to the equal extent as a prior myocardial infarction (MI) in a nondiabetic situation. Studies in hypertensive sufferers have shown always that telmisartan improves insulin sensitivity and lipid profiles. For instance, in patients with kind 2 diabetes (controlled with weight-reduction plan and exercising) and moderate hypertension, telmisartan 40 mg turned into appreciably greater powerful than eprosartan 600 mg in lowering low-density lipoprotein (LDL)-ldl cholesterol, overall cholesterol, and triglycerides(22).

Hypertension and evaluation of alternative antihypertensive medications.

Telmisartan's effectiveness in regulating blood pressure has a long history. Its impact begins to take effect about 3 hours after the first dose (with the greatest blood pressure decrease occurring 4 to 8 weeks after the start of therapy), lasts continuously for 24 hours after dosing, and, importantly, includes the final 4 hours before the next dose. Without changing pulse rate, telmisartan lowers both systolic (SBP) and diastolic (DBP) blood pressure. In several days following a sudden end to therapy, blood pressure gradually returns to pre-treatment levels without rebound hypertension(24).

Uses:

This remedy is used to deal with high blood stress (hypertension). Lowering excessive blood strain allows prevent strokes, coronary heart assaults and kidney issues. It works by using enjoyable arteriole so blood can float greater without difficulty. Used by myself or in aggregate with different instructions of antihypertensives for the remedy of hypertension. Also used inside the remedy of diabetic kidney disease in hypertensive sufferers with kind 2 diabetes mellitus, as well as the treatment of congestive coronary heart failure (only in patients who can not tolerate ACE inhibitors)(16).

Brand Name:

Micardis®(25).

Act Telmisartan 40 80 mg.

Kinzalmono 80 mg(26).

Formulation of telmisartan:

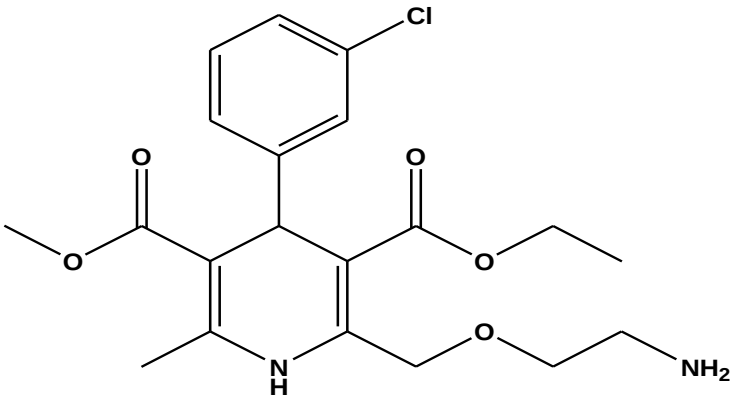
Figure 3 Marketed Formulation of telmisartan

4.2 Amlodipine

Amlodipine is a calcium antagonist. Amlodipine destressed (widens) blood vessels and improves blood flow. It is chemically expressed as 3-ethyl 5-methyl 2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate

Amlodipine is a 3rd generation dihydropyridine calcium antagonist, it is used for the treatment of high blood strain and angina. It was firstly formulated by using Pfizer under the name of Norvasc, and then several generic versions are available now. Amlodipine changed into combined with several drugs to decorate their hobby(27).

Structure



Amlodipine

IUPAC Name

RS)-3-ethyl5-methyl2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4- dihydropyridine-3,5-dicarboxylate.

Class:

Dihydropyridine

Calcium channel blocker:

In the myocardium and vascular involuntary muscle, an essential step in the process of contraction is the entry of calcium ions in the cells. calcium channel blocking drugs or calcium antagonists block the entry of calcium ions into the myocardium and the vascular smooth muscles. thus, myocardial contractility is reduced (negative inotropic effect), the formation and propagation of electrical impulses within the heart is depressed (decreased AV conduction) and coronary and systemic vascular tone is diminished (vasodilitation). Dihydropyridine include nifedipine, amlodipine, nicardipine(28).

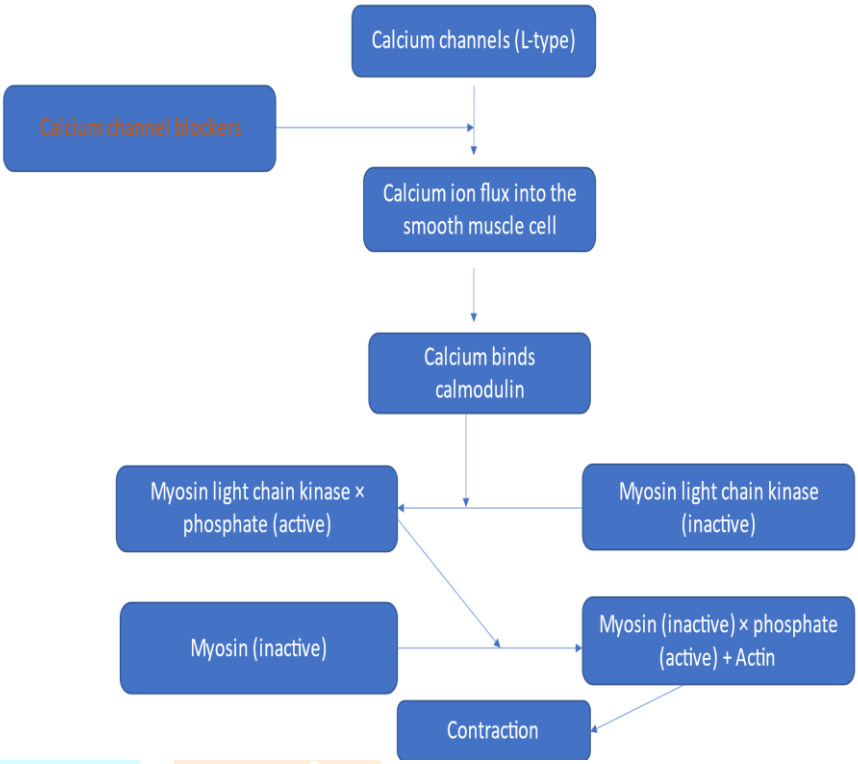


Figure 4 MOA of Amlodipine

Mode of action:

Amlodipine inhibits transmembrane influx of extra-cellular calcium ions across the membranes of myocardial cells and vascular easy muscle cells, without converting serum calcium aggregation. Amlodipine is a fringe blood vessel vasodilator; shows action immediately on involuntary muscle inflicting minimization of peripheral vascular resistance and blood pressure. Total peripheral resistance (afterload) and charge stress product decreases with the treatment of amlodipine and as a result in patients suffering from exertional angina, myocardial oxygen is required at any specified exercise intensity. Amlodipine blocks constriction and restores blood flow in coronary arteries in response to calcium, potassium, epinephrine, serotonin and thromboxane A2 analog in animal research and human vessels in vitro(16). Calcium channel blockers are effective in the elderly and may be selected as monotherapy for patients with Raynaud's phenomenon, peripheral vascular disease, or asthma, as such patients do not tolerate blocker(29).

Pharmacological Profile (Amlodipine)

Long acting dihydropyridine (other members: - nifedipine, nicardipine, isoradipine, nitrendipine & felodipine) Mechanism of action: - coronary and peripheral arterial

Vasodilatation

Dose:

2.5 or 5 grams, single dose (by myself or in

combination with Atenolol)

Adverse consequences: - complications, facial flushing, dizziness,

oedema, gingival hyperplasia

Oral effects:- detectable in gingival crevicular fluid(30).

Solubility:

Soluble in methanol and acetonitrile, sparingly soluble in ethanol and slightly soluble in water(13). Inhibits the influx of calcium ion throughout the mobile membranes selectively with a greater effect on vascular easy muscle cells than on cardiac muscle cells. Serum calcium awareness is not tormented by amlodipine besylate. It has a half-existence of 30- 50 hours. It is used in mixture with different antihypertensives(31).

Side effect profile:

The most typically suggested detrimental impact hindering compliance with amlodipine is peripheral oedema. However, this unfavourable effect can be minimum if the agent is given at bedtime, and decrease doses (2.5 or 5 mg/day) are used. Amlodipine is contains Respectively Indeed, the bedtime administration of nifedipine gastrointestinal therapeutic system was associated with a ninety three percent discount in oedema compared with morning dosing (one percent vs thirteen percent, $p<0.001$,). Other reported facet results encompass dizziness, fatigue, headache, palpitations and nausea, despite the fact that those are generally not bothersome enough to motive discontinuation of the drug. dicated in breastfeeding ladies, cardiogenic shock and volatile angina. Also, Its vasodilatory effect can result in decreased cardiac output in the setting of aortic stenosis(32).

Brand name:

Azor (combination),

Caduet,

Exforge (combination),

Lotrel, Norvasc.

Dose :

5 mg once daily

Adverse Effects :

Headache, oedema, fatigue, dizziness, nausea, palpitation, flushing, muscle cramp, pruritus, and gum hyperplasia(33).

Formulation of telmisartan:

Figure 5 Marketed formulation of amlodipine

Various Methods for analysis of Amlodipine and telmisartan

RP-HPLC method

HPLC Method

Simultaneous spectrophotometric method(14).

5. COMBINATION THERAPY

Combination remedies for the control of hypertension have been available for many years(34). Hypertension treatment generally consists of monotherapy in the first stage, and dual combination therapy at the second stage or higher(35). Compared with monotherapy, a multiple drug or aggregate therapy may additionally result in greater powerful and more set off BP lowering, at decrease doses, with potentially fewer detrimental activities. Sixteen Compared with unfastened combos, constant-dose regimens have the benefits of more comfort and potentially reduced prices, each of which may additionally translate into advanced adherence and advanced BP reductions(36). In Taiwan, the maximum often prescribed antihypertensive medicines are dihydropyridine calcium channel blockers (CCBs). The use of angiotensin II receptor blockers is gaining reputation in Taiwan, while the prescription of angiotensin-changing enzyme inhibitors (ACEIs) is concurrently lowering. There has also been outstanding increase within the use of FDC regimens in hypertension treatment in Taiwan. Therefore, this have a look at aimed to examine the clinical

consequences of free combinations of angiotensin receptor blockers and calcium channel blockers vs food and drug corporation inside the actual world control of high blood pressure(37).

Today, triple combinations are to be had as antihypertensive therapy and are regularly used in lots of nations. In some research, efficacy and protection of calcium channel blocker, angiotensin II receptor blocker (ARB), and diuretic aggregate were shown(38).

Rationale for Combination of a Calcium channel blocker and an Angiotensin receptor blockers :

The cause for using the ACEI/CCB mixtures is to combine drugs with differing mechanisms of movement to provide additive blood strain (BP) lowering whilst minimizing facet consequences which occur with higher doses of the character components. Fixed-dose mixtures should be advanced to either of the individual additives of the product in phrases of BP decreasing efficacy and dose-proscribing facet effects(39). Using separate drugs with complementary mechanisms of movement for the treatment of high blood pressure has lengthy been accepted through physicians. However, the fixed-dose aggregate of two complementary pills turned into slow in gaining reputation(40). Both CCBs and ARBs are effective in lowering BP as monotherapy. The use of these agents in combination has the capability to achieve additive BP reductions by using concentrated on a couple of mechanisms involved in BP law. ARBs intrude with the RAAS via blockading the angiotensin II type 1 receptor and consequently the deleterious consequences of angiotensin II, thereby selling vasodilation and sodium and water excretion. The angiotensin II kind 2 receptor isn't always affected, and it stays uncovered to its agonist angiotensin II, with potentially beneficial vasodilative, anti-inflammatory, and antiproliferative consequences. The peripheral vascular resistance is decreased by CCBs because they inhibit calcium channels in vascular smooth muscle cells. In order to overcome capacity counter-regulatory mechanisms, it is advantageous to target many systems. For example, the compensatory activation of the renin-angiotensin-aldosterone pathway brought on by the use of calcium channel blockers(36). The clinical gain of the combining of a calcium channel blocker and renin angiotensin blockers includes additive blood pressure manipulate, safety from both cardiac and cerebrovascular activities, and an high-quality protection and tolerability profile(41).

Various Methods for analysis of Amlodipine and telmisartan

RP-HPLC method

HPLC Method

Simultaneous spectrophotometric method(14).

Advantages of telmisartan and amlodipine combination therapy:

The current guideline indicate that treatment with two or more antihypertensive agent is important to reap choicest blood pressure for most hypertensive affected person with the intention to reduce cardiovascular threat.

Telmisartan 40 mg +amlodipine five mg (T40/A5) constant-dose combination therapy is expected to acquire tight blood pressure manage because of the robust efficacy and long half-existence of every agent.

Specific drug combinations:

There are numerous antihypertensive medications in each of the seven main classes, which results in a sizable number of potential combinations. In In this position paper, emphasis is placed on 2-drug combinations including classes of pharmacologic drugs (diuretics, CCBs, ACE inhibitors, ARBs, blockers) that lower CV end points(42).

Clinical trials and combined therapy:

The information approximately the advantages and the want of combined therapy comes from numerous medical trials. The ALLHAT trial became designed to evaluate whether or not treatment with an alpha blocker (doxazosin), a CCB (amlodipine), or an angiotensin-converting enzyme I (lisinopril) diminished the prevalence of coronary coronary heart disease or different cardiovascular ailment occasions vs. Treatment with a diuretic (chlorthalidone). In INVEST trial hypertensive coronary artery ailment sufferers elderly 50 years or older were randomly assigned to either calcium antagonist approach (verapamil sustained launch) or a non-calcium antagonist approach (atenolol)(43).

Angiotensin receptor blockers with calcium channel blockers:

Amlodipine besylate is official in IP(44). angiotensin-converting enzyme inhibitor or angiotensin receptor blockers work absolutely additively to lower blood pressure when used with calcium channel blockers. Addition of both of those 2 renin-angiotensin-aldosterone system inhibitors extensively improves the tolerability profile of the calcium channel blockers(42). In order to gain blood pressure control, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of hypertension (JNC 7) advocates 2-drug combos the use of different drug classes in the majority of sufferers. It additionally makes logical sense to combine drugs with unique mechanisms of action such a calcium channel blocker or diuretic, an angiotensin receptor blocker or angiotensin converting enzyme inhibitors. In some studies, these combinations have been found to offer greater BP discounts than the corresponding monotherapies in patients with mild to severe hypertension(45).

Telmisartan/amlodipine safety:

Amlodipine became accepted by using the FDA in July 1992. The first European approval become in July 1989(46). Individually, amlodipine and telmisartan produce a generally incidence of adverse event and are nicely tolerated. The combination can be mainly appropriate for people with diabetes and/or metabolic syndrome as those medications do not get worse the metabolic complications related to their aetiology(47). High-dose telmisartan/low-dose amlodipine and occasional dose telmisartan/excessive-dose amlodipine mixture produced comparable decrease in systolic and diastolic BP values, without a extensive difference between the 2 regimens at any time of the have a look at(19). Telmisartan/ amlodipine as a single-tablet mixture to be had in numerous strengths, validated advanced efficacy to either monotherapy(48). Telmisartan has a different pharmacokinetic profile when compared with other ARBs, and there are few studies examining telmisartan/amlodipine combinations in hypertensive patients(49).

Pharmacology of fixed-combination telmisartan– amlodipine:

Telmisartan is an orally active nonpeptide that lowers BP with once-daily dosing by using blocking off the type I angiotensin II receptor (AT1 receptor), hence selectively inhibiting the pressor effects of the RAS. Telmisartan became authorized with the aid of American FDA (food drug administration) in November 1998 and by means of the European Commission in December 1998 for the treatment of hypertension.

Amlodipine is a dihydropyridine calcium channel blocker that prevents calcium ions from entering cardiac muscle cells and vascular smooth muscle across the membrane. It is a peripheral artery vasodilator that simultaneously relaxes the vascular smooth muscle and lowers blood pressure by reducing peripheral vascular resistance. The pharmacokinetics of repeated oral doses of 80 mg telmisartan at steady kingdom on my own and in combination with Repeated oral doses of amlodipine 10 mg at steady kingdom have been studied in a -manner crossover, open, randomized study design(46).

Pharmacokinetics and pharmacodynamics of telmisartan and amlodipine:

Telmisartan has a bioavailability of about 45% to 50%, whereas amlodipine has a bioavailability of 64% to 90%. Both telmisartan (99%) and amlodipine (93%) have high plasma protein binding. Steady-state blood levels of amlodipine are achieved in 7 to 8 days 49 and in 5 to 7 days for telmisartan.

The half-lives of telmisartan and amlodipine are both quite long, ranging from 20 to 30 hours for the former and 44 hours or longer for the latter. Telmisartan does no longer go through good sized first-skip metabolism, and the majority (about 97%) is removed by biliary-faecal excretion because the figure compound, although a small percent of the drug undergoes glucuronidation. Amlodipine, in contrast, is transformed to inactive metabolites hepatically with approximately 60% excreted as metabolized products and 10% as determine compound in urine. The result of telmisartan and amlodipine coadministration on the

opposite's pharmacokinetic profile is reportedly equivalent to the personally administered compounds, with the two-sided 90% self belief durations for all pharmacokinetic endpoints living inside the general bioequivalence popularity interval (80% to a hundred 25%)(47).

Telmisartan with Amlodipine:

Brand name:

Twynsta (50).

Figure 6 marketed formulations of telmisartan+ amlodipine

6.CONCLUSION:

Hypertension is called 'the silent killer', because it usually has no symptoms. Mean decrease in systolic and diastolic blood pressure achieved by each drug or combination. The combination telmisartan/amlodipine is especially suitable for the treatment of severe hypertension. A fundamental requirement of any combination is evidence that it lowers BP to a greater degree compared with monotherapy with its individual components.

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