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REVIEW ON ANTIHYPERTENSIVE DRUGS

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Abstract:-
With so many different antihypertensive medication classes available, successful treatment of hypertension can be achieved with minimal side effects. Two main topics are covered in this review: the mechanisms of action and adverse effects of the various pharmacological types of antihypertensive medications. To determine which type of hypertension a particular pharmacological class of antihypertensive drug is most indicated for, the mechanism of action is examined using a pharmacological approach, taking into account the molecular receptor targets, the different sites along the arterial system, and the extra-arterial sites of action. One of the biggest global public health issues is hypertension. Among the first-line antihypertensive medications are calcium channel blockers and angiotensin receptor blockers. The study's objective is to gauge how the telmisartan-amlodipine combination responds at different doses of on hypertension.Combining medications with distinct mechanisms of action has emerged as a substitute to boost treatment adherence, lower adverse effects, and improve low blood pressure.[1]

Keywords:-
ACE inhibitor ,Angiotensin Receptor Blocker,Combination therapy,Side Effect,Adverse Effect,Management Of Hypertension.

Introduction:-

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 aliskiren, which was discovered more than ten years ago (2000), pharmacological research has been applied to the treatment of hypertension continuously . A steady pace of discovery has occurred in between, with notable discoveries including spironolactone (1957), beta-blockers (propranolol, 1973), centrally acting alpha-2 adrenergic receptor agonists (clonidine, 1970s), alpha1-adrenergic receptor blockers (prazosin, 1975), calcium channel blockers (verapamil, 1977), angiotensin converting enzyme inhibitors (captopril, 1977), and angiotensin II receptor blockers (losartan, 1993) .[2]

Classification-

Renin angiotensin system inhibitors (RAS):-

i)ACE inhibitors:-Captopril, Enalapril, Lisinopril, Ramipril Perindopril, Benazepril Quinapril,

ii)**Diuretics:-**Thiazides- Hydrochlorothiazide, Furosemide ,Bumetanide

iii)**Direct renin inhibitors**:-Aliskiren

iv)Angiotensin receptor blocker (ARB):- Losartan,condesartan,Telmisartan

v)Calcium channel blockers:- Verapamil, Diltiazen

vi)Vasodilator:- Hydrazine, chlorhydrazine [3]

Mechanism of Action :-

ACE Inhibitors:-

ACE inhibitors have been extensively studied incases and have been shown in double-blind, placebo-controlled trials to lower blood pressure to the same extent as beta-blockers and almost as well as diuretics. drugs in whites but not blacks. ACE inhibitors are well tolerated; side studies and quality of life measures have shown them to be as well or better tolerated than other drugs. Recent double-blind quality of life measures have

not shown that ACE inhibitors are superior to diuretics or at least one type of beta-blocker.

ACE Inhibitors in Diabetes and Renal Disease:-

There are subgroups of patients for whom ACE inhibitors appear to offer significant benefit. Since ACE inhibition has a selective effect on the glomerular afferent artery and reduces arterial resistance, the use of these agents has been shown to be useful in the treatment of patients with proteinuria and diabetic nephropathy. Studies by Parving et al. 1983 (and 1987 reported that in patients with insulin-dependent type 1 diabetes and signs of nephropathy, treatment with a beta-blocker (metoprolol), a vasodilator (hydralazine), central nervous system. agent (methyldopa), a diuretic and a peripheral sympathetic blocker (quanetidine) reduced the decrease in glomerular filtration with a decrease in blood pressure. Other studies. have shown that the use of any antihypertensive medication reduces proteinuria when pressure is lowered, but agents that block the renin-angiotensin system can be particularly effective. [4]

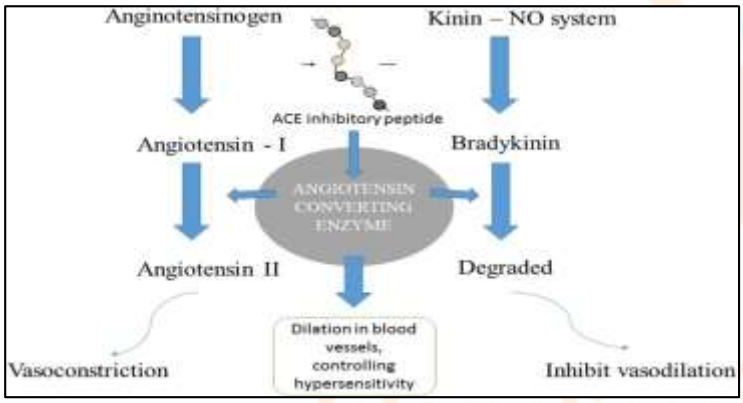

Fig.No.1 Mechanism Of Antihypertensive Activity [5]

- **Diurectic:-**

Amiloride, hypertension, chlorthalidone, eplerenone, hydrochlorothiazide, hypertension, indapamide, potassium-sparing diuretics, sodium chloride symporter inhibitors, spironolactone.Salt-sensitive hypertension occurs when, after addition of sodium, its removal and removal causes a drop in systolic blood pressure (SBP) of 10 mmHg or more. Possible methods to detect salt-sensitive hypertension in routine clinical practice include the use of genetic markers, 4 blood pressure responses to amiloride analogs, 5 and measurements obtained during 24-hour ambulatory monitoring, 6 but none of these methods have achieved widespread acceptance and general acceptance. to use So doctors rely on studies that show the prevalence of salt-sensitive hypertension is higher in blacks, the obese, the elderly and some diabetics.. Recall that comprehensive meta-analyses have indicated that low-dose diuretics have the most evidence and have demonstrated superiority over other antihypertensives, regardless of salt-sensitive status. This is despite the fact that diuretics may be especially helpful in these individuals.

Table 1. Current recommendations and diuretics of the thiazide type Guidelines (released year) Black elderly patients on average.[6]

Guideline (year issued)	Average patient	Blacks	Elderly
Australia (2012) [10]	First line	Not specified	Not mentioned
Canada (2015) [11]	First Line	Thiazide or CCB	Not Said
Europe (2013) [12]	First line	Not specified	Not Stated
International/ASH (2014) [13]	First line	Thiazide or CCB	Not stated
JNC8 (2014) [14]	First line	Thiazide or CCB	Not said
United Kingdom (2011) [15]	ACEi/ARB>>CCB> >ThiazLikea [a]	CCB >> INDAP or CTDN	CCB >> INDAP or CTDN
Resistant HTN (2008) [16]	CTDN, First line	NA	NA
Soc on HTN in Blacks (2010) [17]	NA	CTDN, 1st line	NA

- **Direct renin inhibitors:-**

50 years ago, researchers found that renin inhibition is the best pharmacological approach to block the renin-angiotensin system. Renin is a monospecific enzyme that catalyzes the rate-limiting step in angiotensin II synthesis. When renin and pro-renin bind to the (pro) renin receptor, enzymatic activity increases and further

physiological effects occur. Until recently, the development of clinically effective kidney inhibitors has been difficult. Molecular modeling was used to develop aliskiren, a potent non-peptide direct renin inhibitor of low molecular weight with sufficient bioavailability to achieve sustained suppression of plasma renin activity after oral administration. In hypertensive patients, aliskiren lowers blood pressure in a dose-dependent manner and maintains blood pressure control for 24 hours up to a dose of approximately 300 mg once daily. at these doses, aliskiren is placebo-tolerable.[7]

- **Angiotensin receptor blockers:-**

There are currently 8 drugs commercially available in the United States that have the same property of selectively binding to the angiotensin II AT1 receptor, which is systemically distributed in most tissues throughout the body. Some of the characteristics of these drugs and their combinations with either thiazide-type diuretics (hydrochlorothiazide [HCT] or chlorthalidone [CLD]) or with amlodipine in fixed-dose formulations are summarized in Table I. Other drugs that meet the pharmacological criteria for ARBs, But are still under investigation or have never been marketed in the US due to toxicity.[8]

- **Calcium Channel blockers:-**

Calcium channel blockers are effective and generally well tolerated blood pressure agents. Their long duration of action and favorable side effect profile are advantages and they are very widely used. In observational studies, CCBs are prescribed to 30-40% of hypertensive patients, and their frequency of use is increasing. When used as monotherapy, CCBs appear to be equivalent or superior to other classes of agents for lowering blood pressure. Although the data are not entirely consistent, when used as monotherapy, they are no better and may be worse than alternative agents, particularly beta-blockers, ACE inhibitors and diuretics, in reducing cardiovascular morbidity and mortality, with the possible exception of dihydropyridines to reduce stroke. Risk However, they are effective in reducing CVD when used in combination with other agents, such as ACE inhibitors, targeting aggressive blood pressure targets.[9
]

- **Vasodilators:-**

Pregnancy:-

Although classified as pregnancy category C, hydralazine has been used to treat hypertension during pregnancy for several decades, and has been cited as the most commonly used drug for acute hypertension in the population.Several small comparative studies have found both intravenous (IV) hydralazine and labetalol to be effective in acute maternal to lower blood pressure. Although results were conflicting as to which agent lowered blood pressure the most, each study concluded that both hydralazine and labetalol were effective treatment options. Maternal. reflex tachycardia has been observed with hydralazine therapy. Fetal heart rate may not be affected, but fetal distress has been reported with antenatal hydralazine. Hydralazine has also been shown to be as effective as DHP-CCB in controlling blood pressure; however, nifedipine can reach blood pressure more quickly, with lower doses and a longer duration.[10]

- **Management of Hypertension:-**

Hypertension affects approximately one in three adults in the United States, and approximately 2 million new cases are diagnosed each year. In addition, 28% of the US population has prehypertension, and approximately 7% of Americans do not know they have it. . Even high blood pressure.Hypertension affects more than one billion people worldwide and is predicted to increase to 1.56 billion by 2025.It is the leading cause of death and the second leading cause of disability-related life years worldwide. Randomized controlled clinical trials have shown that that controlling hypertension reduces the risk of stroke, coronary artery disease, heart failure, end-stage renal disease, peripheral vascular disease and mortality.The risk of developing these complications is continuous, starting with hypertension. (BP) as low as 115/75 mm Hg. Chronic kidney disease, coarctation of the aorta, Cushing's syndrome, obstructive sleep apnea,drugs, pheochromocytoma Primary hyperaldosteronism, renovascular disease, thyroid/parathyroid disease.[11]

Screening Effect on Antihypertensive Activity:-

In -vitro animal models:-

Endothelin receptor antagonism in isolated porcine hearts:-

Endothelins (ET) are involved in the pathogenesis of cardiovascular disease. Arterial smooth muscle contains ETA receptors, so this model uses an isolated porcine coronary artery. ET causes strong, long-lasting contractions in individual blood vessel walls. Endothelin peptides increase blood pressure in both in vitro and in vivo studies. The study includes six 12-week-old crossbred pigs (30-40 kg). Ketamine (0.2 mg/kg/min) and xylazine (0.03 mg/kg/min) are used to sedate pigs. The heart is exposed through a left thoracotomy. The left anterior descending coronary artery is isolated from a porcine heart. Before cleaning, fat and connective tissue

are removed. Endothelialized arteries are cut into spiral strips 10 mm long and 1 mm wide. To remove the vascular endothelium, the inner surface of the spiral rings is gently rubbed with filter paper. At 37 °C, each strip is suspended in Krebs-Henseleit solution bubbled with 95% O 2/5% CO. After stabilization of the isolated preparation, isometric contraction is achieved with 50 mM KCl. ET-1 concentration response curves are obtained by cumulative addition of ET-1. The endothelin receptor antagonist/test drug is added to theorgan bath twenty minutes before the addition of ET-1 and a concentration-response curve is recorded. Analysis of Schild plots gives pA, values and slope.

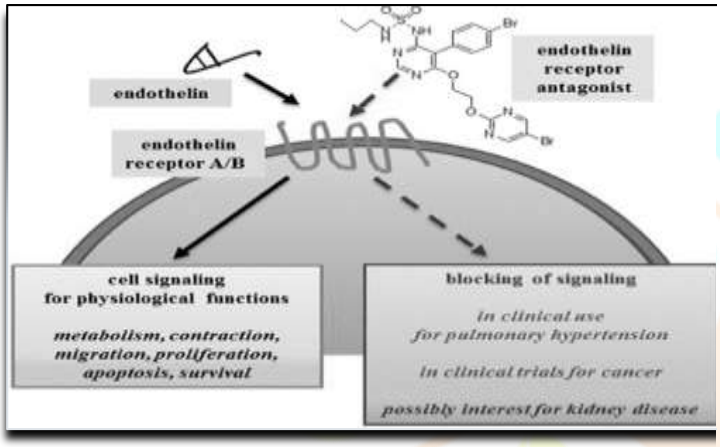

Fig. No.2 Endothelin Receptor Antagonism Method[12]

- **Combination Therapy:-**

The ability to maintain constant or nearly constant blood pressure in response to various stressors is central to homeostasis, and the human body has additional physiological mechanisms to regulate arterial pressure. Blood pressure is primarily determined by three factors: renal sodium excretion and resulting plasma and total body volume, cardiac efficiency and vascular tone. 6 These factors regulate intravascular volume, cardiac output, and systemic vascular resistance, which are direct hemodynamic determinants of blood pressure. Both the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) are intimately involved in the real-time regulation of these parameters. In addition, genetic makeup, diet and environmental factors affect the blood pressure of individual patients.[13]

- **Pregnancy in Hypertension:-**

Pregnancy-induced hypertension (PIH): After 28 weeks of gestation, pregnant women attending the maternity unit with high blood pressure (≥140/90 mmHg) were measured twice at six-hour intervals with or without proteinuria by trained data collectors. The diagnosis of PIH was confirmed by a doctor working in the maternity ward. Pregnancy-induced hypertension includes gestational hypertension, preeclampsia, and eclampsia.[14]

- **Side effects of Hypertension:-**

(i)Diuretics:-

These high blood pressure medications remove excess water and sodium (salt) from your body. Diuretics can cause the following side effects: Excessive urination. Extra water means more time in the bathroom. Take these medications earlier in the day and when you are not far from the bathroom. Erectile dysfunction in some men Weakness, leg cramps or fatigue. Diuretics can lower the body's levels of the mineral potassium, which can lead to these side effects. However, certain potassium-sparing diuretics do not have this effect. Severe and sudden leg pain, which is a symptom of gout it is rare.

(ii)Beta-Blockers:-

Beta blockers make your heart beat less hard and slower. These medications can cause side effects such as: asthma symptoms, cold hands and feet, depression, hypertension High Blood Pressure Guide Side Effects of High Blood Pressure Medications. As an informed patient, read what medication you are taking. and its possible side effects. You can find the full list in your medication list. To get you started, here's an overview of the most common side effects of hypertension medications. Medicines used to treat high blood pressure.

(iii)Angiotensin Converting Enzyme (ACE) Inhibitors:-

These high blood pressure medications prevent the production of a hormone that causes blood vessels to constrict, causing the blood vessels to relax. ACE inhibitors can cause the following side effects: Dry, hacking cough that does not go away. If you experience this side effect, your doctor may prescribe a different

type of medication. Rash and loss of taste are two other possible side effects of ACE inhibitors.

(iv)Angiotensin II Receptor Blockers (ARBs):-

These high blood pressure medications protect blood vessels from a hormone that narrows blood vessels. This allows the blood vessels to remain open. One of the most common side effects of ARBs is dizziness, allergies, arthritis, atrial fibrillation, breast cancer, cancer, Crohn's disease, depression, diabetes.

(v)Beta-Blockers:-

Beta blockers make your heart beat less hard and slower. These medicines can cause side effects such as: asthma symptoms, cold hands and feet, depression, erectile dysfunction, insomnia and sleep disturbances.

(vi)Angiotensin Converting Enzyme (ACE) Inhibitors:-

These high blood pressure medications prevent the production of a hormone that causes blood vessels to constrict, causing the blood vessels to relax. ACE inhibitors can cause the following side effects: Dry, hacking cough that does not go away. If you experience this side effect, your doctor may prescribe a different type of medication. Rash and loss of taste are two other possible side effects of ACE inhibitors.

(vii)Angiotensin II Receptor Blockers (ARBs):-

These high blood pressure medications protect blood vessels from a hormone that narrows blood vessels. This allows the blood vessels to remain open. One of the most common side effects of ARBs is dizziness.

(viii)Calcium Channel Blockers (CCBs):-

These high blood pressure drugs prevent calcium from entering the cells of the heart muscle and blood vessels. The blood vessels can then relax. CCBs can cause the following side effects :Constipation Dizziness Headache Irregular or very fast heartbeat (palpitations) Swelling of the ankles Alpha blockers.Dry cough that does not go away. If you experience this side effect, your doctor may prescribe a different type of medication. Rash and loss of taste are two other possible side effects of ACE inhibitors.[9]

(ix)Vasodilators:-

Vasodilators relax the muscles in the blood vessels, open the blood vessels and improve blood flow. These medicines can cause:Excessive hair growth, fluid retention, headache, irregular or very fast heartbeat (palpitations), joint pain, swelling around the eyes.

(x)Renin Inhibitor:-

This newer class of high blood pressure medication reduces chemicals that constrict blood vessels. This medicine can be used alone or in combination with another medicine. Side effects may include Cough, diarrhea or abdominal pain, heartburn, rash.[15]

- **Adverse effects of Hypertension:-**

Diuretics increase potassium excretion and can cause hypokalemia (low potassium in the blood), which contributes to irregular heartbeats and muscle weakness. However, the combination of a thiazide or loop diuretic with a distal potassium-sparing agent (as in the combination drugs Maxzide or Mouretic) prevents potassium loss and eliminates this problem. Diuretics slightly increase the level of uric acid and generally should not be used in patients with gout. They cause a small increase in blood sugar, but it is not clear whether this promotes diabetes in the long term. Excessive diuretic therapy can cause low blood pressure, orthostatic hypotension (weakness, dizziness and possibly fainting when standing), and feelings of fatigue and lethargy, all of which can be prevented or reversed by withholding the diuretic for a day or two and continuing with. lower dose if needed. Side Effects: The most common side effects of beta blockers are: slow heart rate, depression and irritability, sleep disturbances, decreased exercise tolerance, increased wheezing and asthma, sexual dysfunction, and serum potassium (hyperkalemia). These effects are mostly dose-dependent and the dose can be reduced if they occur are mostly dose-dependent and the dose can be reduced if they occur reduced if they occur. [16]

Contraindication :-

COMPELLING AND POSSIBLE CONTRAINDICATIONS[a] TO ANTIHYPERTENSIVE DRUGS		
DRUG CLASS	**COMPELLING**	**POSSIBLE CONTRAINDICATION/PRECAUTION**
Diuretics (thiazides)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcemia Hypokalemia Erectile dysfunction
Mineralocorticoid receptor antagonists (MRA)	Hyperkalemia Serum creatinine >2.5 mg/dL in men, >2.0 mg/dL in women)	Situations associated with higher risk of hyperkalemia (ACEI, ARB, diabetes)
ACE inhibitors	Pregnancy Angioneurotic edema Hyperkalemia Bilateral renal artery stenosis	Women with child-bearing potential
Angiotensin receptor blockers	Pregnancy Hyperkalemia Bilateral renal artery stenosis	Women with child-bearing potential
Ca^{2+} channel blockers (dihydropyridines)		Tachycardia/arrhythmia Heart failure
Ca^{2+} channel blockers (verapamil, diltiazem)	AV block (grade 2-3) Severe LV dysfunction Heart failure	Co-medication with CYP3A4- or Pgp–dependent drugs (e.g. statins, digoxin)
β Blockers	Asthma AV block (grade 2-3)	Metabolic syndrome Glucose intolerance Athletes and physically active patients Chronic obstructive lung disease Psoriasis Depression
α Blockers	Heart failure	
Central sympatholytic drugs	Depression AV block (grade 2-3)	Erectile dysfunction Xerostomia

Table No.2 Contraindications Of Antihypertensive Activity[17]

- **Conclusion:-** The ongoing challenges of hypertension management continue to require special attention. Several national and international guidelines have been published for the treatment of hypertension, emphasizing mono or combination therapy according to blood pressure levels and related comorbidities. Globally, treatment strategies for hypertension have varied greatly over time depending on the initial drug, from diuretics to ACEI/ARB/CCB, from monotherapy to low-dose combination therapy with single pills. National health policy makers should consider the evaluation and treatment of hypertension in the national health system right to achieve better results in terms of hypertension mortality and mortality. Many clinical trials have examined assessment model, patient adherence, physician adherence to hypertension treatment guidelines, cost implications, and other comorbidity data. Despite this information and published guidelines, there are inconsistencies in therapy management, sometimes forcing clinicians to individualize therapy based on patient characteristics and response. In developing countries such as India, more systematic studies are needed to assess prescribing patterns and use of guideline-based antihypertensive medications that can be tailored to patients.[18]

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