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A Review on Sacubitral/Valsartan drug for medication and preventation of Cardiovascular Disease

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ABSTRACT:-

Cardiovascular (CV) disease is a major cause of morbidity and mortality in the developing and the developed world. Mortality from CV disease had plateaued in the recent years raising concerning alarms about the sustained efficacy of available preventive and treatment options. Sacubitril/Valsartan is a much needed therapeutic advance in the avenue oh CV disease.It may help to live longer and lower chance of having to go to hospital for heart failure. This product contain 2 medications: Sacubitral and Valsartan. Sacubitril belongs to a class of drug called Neprilysin inhibitors and Valsartan belongs to a class of drug called Angiotensin receptor blockers (ARBs). They work by relaxing blood vessels, so that blood can flow more easily, which makes it easier for our heart to pump blood to our body. This product should not be taken with ACE inhibitors (such as captopril, enalapril), since our risk of serious side effects may increase. Do not take this product for at least 36 hours before or after taking ACE.

KEYWORDS:- Angiotensin converting enzyme inhibitors, Heart failure, Sacibitril/Valsartan, Reduced ejection fraction, Cardiovascular.

INTRODUCTION:-

Cardiovascular (CV) disease is major cause of morbidity and mortality in the developing and the developed world, and represents a major barrier to sustainable human development [1,2]. Ischemic heart disease, cerebrovascular disease and hypertension among others represents major forms of CV disease.It is characterized at the myocardial level by ventricular remodeling and dysfunction [3,4] and clinically, by pump failure and sudden death. It is major global public health problem affecting an estimated 26 million people around the world [5].

Sacubitril/Valsartan is a first in class angiotensin receptor neprilysin inhibitor (ARNi) approved for the treatment of HF. It consists of the angiotensin receptor blocker (ARB) 'valsartan' and the neprilysin inhibitor 'sacubitril', in a 1:1 mixture by molecule count. The combination is thereby marketed as an ''Angiotensin Receptor- Neprilysin Inhibitors'' [6].

Sacubitril:-

Sacubitril inhibit the enzyme Neprilysin which is responsible for degradation of Natriuretic peptide this increase in the serum natriuretic peptide level. Natriuretic peptide have multiple effect directed mainly on the reduction of blood pressure one decrease in the pre and afterload.

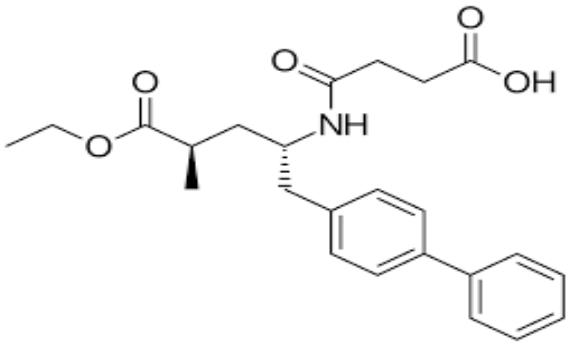

Fig 1. Structure of Sacubitril

Natriuretic peptide reduce the reabsorption of sodium and fluid in the kidney also the peptide result in the dilation of afferent glomerular arterioles constriction of the efferent glomerular arterioles leading to the increase in glomerular filtration rate. Natriuretic peptide inhabit the secretion of renin ,resulting in the prevention of activation of the renin- angiotensin –aldosterone- system(RAAS).This led to the reduction of aldosterone secretion aldosterone cause the reabsorption of sodium and water into the blood and secretion of potassium into the urine. Natriuretic peptide relax vascular smooth muscles in the arterioles and venules ,prevents the ventricular hypotrophy natriuretic peptides are degrade under the influence of a neutral endopeptidase neprilysin. Sacubitrial increase serum level of natriuretic peptide by the inhabitation of neprilysin but, if sacubitril is used without additional inhabitation of renin-angiotensin-aldosterone-system (RAAS),the excessive aldosterone is secreted for its prevention sacubitrial is combined with valsartan.

Valsartan:-

Valsartan is Angiotensin II receptor blockers in order to better understand the mechanism of action is well talk about Renin –Angiotensin-Aldosterone-System(RAAS). Juxtaglomerular cells release renin in response to decrease in afferent arteriole pressure reduce sodium chloride deliver to macula densa increase sympathetic tone renin cleaves a decapeptide in angiotensin I from angiotensinogen.Angiotensin I is transformed in angiotensin II by angiotensin converting enzyme also called ACE, which is synthetize mainly in the lungs ,angiotensin II is the strongest vasoconstrictive effect, it cause aldosterone release in the adrenal cortex leading to the sodium and fluid retention and potassium execration and impaired endothelial cell function also angiotensin II cause the release of vasopressin exhibiting reabsorption of water in kidney and it has vasoconstrictive effect ,also vasopressin enhance the sensation of thrust, angiotensin II stimulate sodium hydrogen exchangers increase sodium reabsorption.

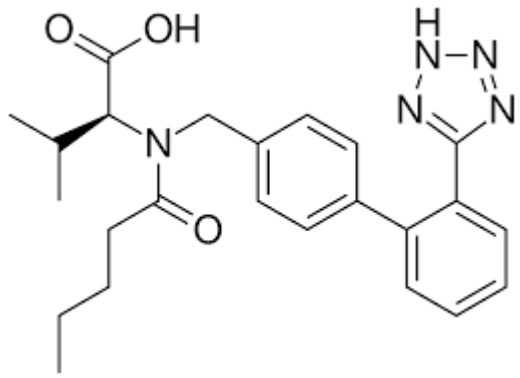

FIG 2. Structure of Valsartan

All these mechanism leads to an increase in both blood volume and vascular tone result in elevated blood pressure also this result in increase afterload, afterload is the pressure against which the heart pump the blood during ventricular systole if afterload is raised, the ventricle must create a higher tension to eject the same volume of blood compared to the normal heart. Valsartan inhabits angiotensin II receptor blocker present undesirable effect of angiotensin ,thus it has the vasodilating properties prevention an excessive aldosterone secretion reducing sodium and fluid retention and also, it reduce the pre and afterload.

MECHANISM OF SACUBITRIL & VALSARTAN:-

SACUBITRIL:-

Sacubitril is a prodrug that is activated to sacubitrilat (LBQ657) by de-ethylation via esterases[7]. Sacubitrilat inhibits the enzyme neprilysin[8] which is responsible for the degradation of atrial and brain natriuretic pe1tide, two blood pressure–lowering peptides that work mainly by reducing blood volume [9]. In addition, neprilysin degrades a variety of peptides including bradykinin [10] an inflammatory mediator, exerting potent vasodilatory action.

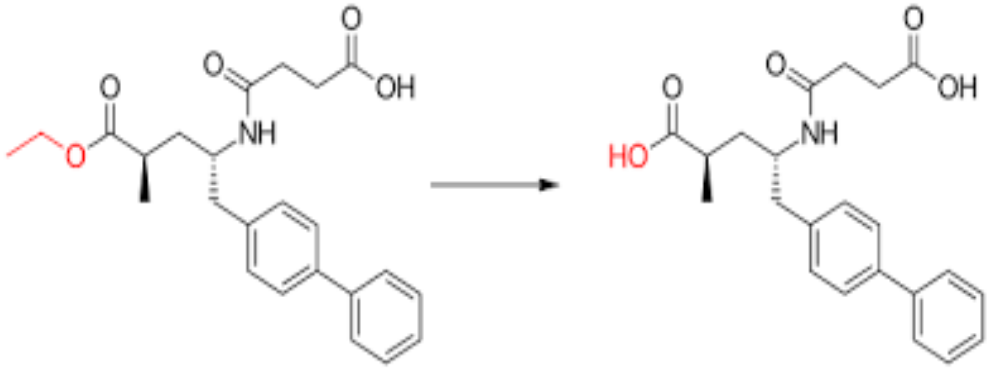

Fig 3. Sacubitril activation to sacubitrilat

VALSARTAN:-

Valsartan blocks the actions of angiotensin II, which include constricting blood vessels and activating aldosterone, to reduce blood pressure [11]. The drug binds to angiotensin type I receptors (AT1), working as an antagonist. This mechanism of action is different than that of the ACE inhibitor drugs, which block the conversion of angiotensin I to angiotensin II. As valsartan acts at the receptor, it can provide more complete angiotensin II antagonism since angiotensin II is generated by other enzymes as well as ACE. Also, valsartan does not affect the metabolism of bradykinin like ACE inhibitors do [11].

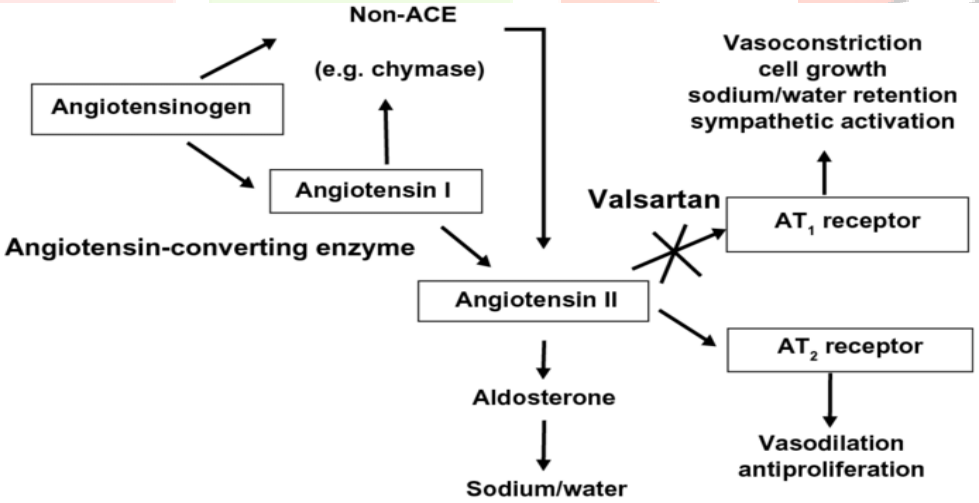

Fig 4. Mechanism of Valsartan

PHARAMACOLOGY OF SACUBITRIL/VALSARTAN:-

Valsartan blocks the angiotensin II receptor type 1 (AT1). This receptor is found on both vascular smooth muscle cells, and on the zona glomerulosa cells of the adrenal gland which are responsible for aldosterone secretion. In the absence of AT1 blockade, angiotensin causes both direct vasoconstriction and adrenal aldosterone secretion, the aldosterone then acting on the distal tubular cells of the kidney to promote sodium reabsorption which expands extracellular fluid (ECF) volume. Blockade of (AT1) thus causes blood vessel dilation and reduction of ECF volume.[12,13]

Sacubitril is a prodrug that is activated to sacubitrilat (LBQ657) by de-ethylation via esterases.[14]. Sacubitrilat inhibits the enzyme neprilysin[15] a neutral endopeptidase that degrades vasoactive peptides,including natriuretic peptides, bradykinin, and adrenomedullin. Thus, sacubitril increases the levels of these peptides, causing blood vessel dilation and reduction of ECF volume via sodium excretion[16].

Neprilysin also has a role in clearing the protein amyloid beta from the cerebrospinal fluid, and its inhibition by sacubitril has shown increased levels of AB1-38 in healthy subjects (Entresto 194/206 for two weeks). Amyloid beta is considered to contribute to the development of Alzheimer's disease, and there exist concerns that sacubitril may promote the development of Alzheimer's disease.[17,18].

MEDICAL USES:-

Sacubitril/valsartan can be used instead of an ACE inhibitor or an angiotensin receptor blocker in people with heart failure and a reduced left ventricular ejection fraction (LVEF)[19,20] alongside other standard therapies (e.g. beta-blockers) for heart failure [21,22]. To investigate its use for heart failure in those with a preserved LVEF (HFpEF), Novartis funded the PARAGON-HF trial which was designed to investigate the use of sacubatril/valsartan in the treatment of HFpEF patients with a LVEF of 45% or more. Concluding in 2019, it failed to show significance for reducing hospitalisation related to heart failure or reducing death from cardiovascular causes, and therefore appearing to show limited benefit to those with HFpEF.

CONCLUSION:-

From the above information we have conclude that sacubitril/valsartan improves the symptoms for patients. During this mechanism different regulatory bodies have different criteria for considering sacubitril/valsartan.

REFERENCE:-

1.Roth GA, Johnson C, Abajobir A, et al. Global regional, and national burden of cardiovascular disease for 10 cause, 1990 to 2015; 70:1-25.

2.Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics 2016 update: a report from the American Heart Association. Circulation 2016; 133:e38-e360.

3.Cheng, S. & Vasan, R.S Advances in the epidemiology of heart failure and left ventricular remodeling. Circulation 124, 516-519 (2011).

4.Mann, D.L & Bristow, M.R. Mechanisms and models in heart failure: the biomechanical model and beyond. Circulation 111, 2837-2849 (2005).

5.Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev 2017; 3:7-11.

6.Fala L. Entresto: first in class angiotensin receptor neprilysin inhibitor FDA approved for patients with heart failure. Am Health Drug Benefits. 2015; 8(6) 330-334.

7. Solomon SD. "HFpEF in the Future: New Diagnostic Techniques and Treatments in the Pipeline". Boston. p. 48. Retrieved 2012-01-26.

8. Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, et al. (April 2010). "Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi)". Journal of Clinical Pharmacology.

9. Schubert-Zsilavecz M, Wurglics M. "Neue Arzneimittel 2010/2011" (in German).

10. Entrez Gene: Membrane metallo-endopeptidase"[17:45, 9/24/2020] Patil: Entresto- sacubitril and valsartan tablet, film coated".

11. Mutschler E, Schäfer-Korting M (2001). Arzneimittelwirkungen (in German) (8 ed.). Stuttgart: Wissenschaftliche Verlagsgesellschaft. p. 579

12. Zouein FA, de Castro Brás LE, da Costa DV, Lindsey ML, Kurdi M, Booz GW (2013). "Heart Failure with Preserved Ejection Fraction". J. Cardiovasc. Pharmacol. 62 (1).

13. Solomon SD. "HFpEF in the Future: New Diagnostic Techniques and Treatments in the Pipeline". Boston. p. 48. Retrieved 26 January 2012.

14. Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, Maahs S, Ksander G, Rigel DF, Jeng AY, Lin TH, Zheng W, Dole WP (2010). "Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi)". J Clin Pharmacol. 50 (4): 401–408.

15. Schubert-Zsilavecz M, Wurglics M. "Neue Arzneimittel 2010/2011.

16. Patel N, Gluck J (2017). "Is Entresto good for the brain?". World J Cardiol. 9(7): 594–599.

17. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, et al. (27 September 2016). "2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America". Circulation. 134 (13).

18. Hubers SA, Brown NJ (March 2016). "Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition". Circulation. 133 (11): 1115–1119.

19. FDA approves new drug to treat heart failure" (Press release). U.S. Food and Drug Administration (FDA). 7 July 2015. Archived from the original on 26 January 2018.

20. Chang HY, Chen KC, Fong MC, Feng AN, Fu HN, Huang KC, et al. (September 2019). "Recovery of left ventricular dysfunction after sacubitril/valsartan: predictors and management". J Cardiol. 75 (3): 233–241.

21. McMurray JJ, et al. (30 August 2014). "Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure". N Engl J Med. 371 (11): 993–1004.

22. Solomon SD, McMurray JJ, Anand IS, Ge J, Lam CS, Maggioni AP, et al. (October 2019). "Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction" (PDF). New England Journal of Medicine. 381(17): 1609–1620.