Lecture-4- **د.رياض الموسوي**

Heart Failure

Heart failure (HF) is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body. Its cardinal symptoms are dyspnea, fatigue, and fluid retention. HF is due to an impaired ability of the heart to adequately fill with and/or eject blood. It is often accompanied by abnormal increases in blood volume and interstitial fluid.

Compensatory physiological responses in HF

The failing heart evokes three major compensatory mechanisms to enhance cardiac output. Although initially beneficial, these alterations ultimately result in further deterioration of cardiac function.

1- Increased sympathetic activity:

2- Activation of the renin-angiotensin system

3- Myocardial hypertrophy:

Pharmacological treatment in HF :-

A- ***ACEIs :-***

Actions on the heart:

1-ACE inhibitors decrease vascular resistance, venous tone, and blood pressure, resulting in an increased cardiac output.

2-ACE inhibitors also blunt the usual angiotensin II mediated increase in epinephrine and aldosterone seen in HF.

3- ACE inhibitors improve clinical signs and symptoms in patients also receiving thiazide or loop diuretics and/or digoxin.

4- The use of ACE inhibitors in the treatment of HF has significantly decreased both morbidity and mortality.

Indications:-

1- ACE inhibitors may be considered for single-agent therapy in patients who present with mild dyspnea on exertion and do not show signs or symptoms of volume overload.
2- Asymptomatic HF with LVF.
3- Patient had recent MI with HF.

Pharmacokinetics: All ACE inhibitors are adequately but incompletely absorbed following oral administration. The presence of food may decrease absorption, so they should be taken on an empty stomach. Except for captopril, ACE inhibitors are prodrugs that require activation by hydrolysis via hepatic enzymes. Renal elimination of the active moiety is important for most ACE inhibitors, an exception being fosinopril. Plasma half-lives of active compounds vary from 2 to 12 hours, although the inhibition of ACE may be much longer. The newer compounds such as ramipril and fosinopril require only once-a-day dosing.

B- ***ARBs*** **:-**

Actions on the cardiovascular system: All the ARBs are approved for treatment of hypertension based on their clinical efficacy in lowering blood pressure and reducing the morbidity and mortality associated with hypertension. As indicated above, their use in HF is as a substitute for ACE inhibitors in those patients with severe cough or angioedema.

Pharmacokinetics: All the drugs are orally active and require only once-a-day dosing. Losartan, the first approved member of the class, differs from the others in that it undergoes extensive first-pass hepatic metabolism, including conversion to its active metabolite. The other drugs have inactive metabolites.

Elimination of metabolites and parent compounds occurs in the urine and feces; the proportion is dependent on the individual drug. All are highly

plasma protein-bounding (greater than 90 percent) and, except for candesartan, have large volumes of distribution.

S.E:- of ACEIs & ARBs discussed previously.

C- ***β-Blockers :-***

Although it may seem counterintuitive to administer drugs with negative inotropic activity to a patient with HF, several clinical studies have clearly demonstrated improved systolic functioning and reverse cardiac remodeling in patients receiving β-blockers.

Benefits of β-blockers in HF:-

1- Decreasing the heart rate and inhibiting the release of renin.
2- Prevent the direct deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy and cell death.

Two β-blockers have been approved for use in HF: Metoprolol (selective β1-blocker) and Carvedilol (non-selective β1,β2, α1 blocker) , they reduce morbidity and mortality associated with HF. Treatment should be started at low doses and gradually titrated to effective doses based on patient tolerance.

D- ***Diuretics :-***

Diuretics relieve pulmonary congestion and peripheral edema. These agents are also useful in reducing the symptoms of volume overload, including orthopnea and paroxysmal nocturnal dyspnea. Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases the cardiac workload and the oxygen demand. Diuretics may also decrease afterload by reducing plasma volume, thus decreasing blood pressure. Thiazide diuretics are relatively mild diuretics and lose efficacy if patient creatinine clearance is less than 50 mL/min. Loop diuretics are used for patients who require extensive diuresis and those with renal insufficiency.

E- Direct Vasodilators

Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing the venous capacitance; arterial dilators reduce systemic arteriolar resistance and decrease afterload. Nitrates are commonly employed venous dilators for patients with congestive HF. If the patient is intolerant of ACE inhibitors or β-blockers, the combination of hydralazine and isosorbide dinitrate is most commonly used. [Calcium-channel blockers should be avoided in patients with HF.]

F- Spironolactone

Patients with advanced heart disease have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone. Spironolactone is a direct antagonist of aldosterone, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia. Spironolactone therapy should be reserved for the most advanced cases of HF. Because spironolactone promotes potassium retention, patients should not be taking potassium supplements. Adverse effects include gastric disturbances, such as gastritis and peptic ulcer; central nervous system effects, such as lethargy and confusion; and endocrine abnormalities, such as gynecomastia, decreased libido, and menstrual irregularities.

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