Cardiovascular Drugs

Fb/Nurse-Info

1. What is CHF?

- Occurs when cardiac output is insufficient to meet the demands of tissue perfusion.
- It may primarily be due to systolic dysfunction or diastolic dysfunction.

A. Systolic dysfunction:

- The ventricles are dilated and unable to develop sufficient wall tension to eject adequate quantity of blood.
- Occurs in ischaemic heart disease, valvular incompetence, dilated cardiomyopathy, myocarditis, tachyarrhythmias.

B. Diastolic dysfunction:

Ventricular wall is thickened and unable to relax properly during diastole; ventricular filling is impaired because of which output is low. Observed in hypertension, aortic stenosis, congenital heart disease, A-V shunts, hypertrophic cardiomyopathy.

What are the Goals of drug to treat CHF?

2 distinct goals:

(a) Relief of congestive/low output symptoms and restoration of cardiac performance,

- ***Inotropic drugs***- digoxin, dobutamine,dopamine,
- ***Diuretics***-furosemide, thiazides
- ***Vasodilators***-ACE inhibitors/ AT1 antagonists, hydralazine, nitrate, nitroprusside
- ***Beta Bloocker***- Metoprolol, bisoprolol

(b) Arrest/reversal of disease progress and prolongation of survival:

- ACE inhibitors/AT1 antagonists
- Beta blockers
- Aldosterone antagonist- Spironolacton::

A. Angiotensin-converting enzyme inhibitors

- Part of standard pharmacotherapy.
- Block the enzyme that cleaves angiotensin I to vasoconstrictor angiotensin II (potent vasoconstrictor).
- They also diminish the inactivation of bradykinin (a potent vasodilator).
- Hence Vasodilation occurs

1. Actions on the heart:

Decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output.

ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HF.

2. Indications:

- ACE inhibitors may be considered for patients with asymptomatic and symptomatic CHF.
- Importantly, ACE inhibitors are indicated for patients with all stages of left ventricular failure.
- Patients with the lowest ejection fraction show the greatest Benefit from use of ACE inhibitors.
- Depending on the severity of HF, ACE inhibitors may be used in combination with diuretics, β-blockers,*digoxin, aldosterone antagonists, and hydralazine/isosorbide dinitrate fixed-dose combination.*

B. Angiotensin receptor blockers (ARBs)

- Orally active compounds, competitive antagonists of the angiotensin II type 1 receptor.
- ARBs have the advantage of more complete blockade of angiotensin II action, because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II.
- ARBs do not affect bradykinin levels.
- Although ARBs have actions similar to those of ACE inhibitors,they are not therapeutically identical.
- ARBs are a substitute for ACE inhibitors in those patients who cannot tolerate the latter.

1. Actions on the cardiovascular system:

- **Action of ARBs and** ACE inhibitors on preload and afterload are similar.
- Their use in HF is mainly as a substitute for ACE inhibitors in those patients with severe cough or angioedema, which are thought to be mediated by elevated bradykinin levels.
- ARBs are also used in the treatment of hypertension

2. Adverse effects:

- ARBs have an adverse effect and drug interaction profile similar to that of ACE inhibitors.
- However, the ARBs have a lower incidence of cough and angioedema. Like ACE inhibitors, ARBs are contraindicated in pregnancy.

C. Aldosterone antagonists

- 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.
- ***Eplerenone*** *is a* competitive antagonist of aldosterone at mineralocorticoid receptors.
- Although similar in action to *spironolactone at the mineralocorticoid* receptor, *eplerenone has a lower incidence of endocrine-related* side effects due to its reduced affinity for glucocorticoid, androgen, and progesterone receptors.
- Aldosterone antagonists are indicated in patients with more severe stages of CHF and recent myocardial infarction.

II. β- Blockers

1. It has negative inotropic activity in HF, BUT it improves systolic functioning and reverse cardiac remodeling in patients receiving.
2. Occasionally initial exacerbation of symptoms were observed.
3. It prevent the changes that occur because of chronic activation of the sympathetic nervous system.
4. These agents decrease heart rate and inhibit release of renin in the kidneys.
5. Prevent the deleterious effects of norepinephrine on the cardiac muscle fibers,decreasing remodeling, hypertrophy, and cell death.
6. Three β-blockers have shown benefit in HF: bisoprolol, carvedilol, and long-acting metoprolol succinate.

III. Diuretics

1. It relieve pulmonary congestion and peripheral edema,also useful in reducing the symptoms of volume overload,including orthopnea and paroxysmal nocturnal dyspnea.
2. Decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases cardiac workload and oxygen demand.
3. Diuretics may also decrease afterload by reducing plasma volume, thereby decreasing blood pressure.

1. Loop diuretics are the most commonly used diuretics in HF.
2. These agents are used for patients who require extensive diuresis and those with renal insufficiency.
3. Overdoses of loop diuretics can lead to profound hypovolemia.
4. As diuretics have not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess.

IV. Vasodilators

1. Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance.

2. Nitrates are commonly used venous dilators to reduce preload for patients with chronic HF.

3. Arterial dilators, such as hydralazine reduce systemic arteriolar resistance and decrease afterload.

4. If the patient is intolerant of ACE inhibitors or β-blockers, or if additional vasodilator response is required, a combination of hydralazine and isosorbide dinitrate may be used.

5. Adverse effects: Headache, hypotension,and tachycardia are common adverse effects with this combination.

V. Inotropic agents

- Positive inotropic agents enhance cardiac contractility and, thus,increase cardiac output.
- All positive inotropes in CHF have been associated with reduced survival, especially in patients with CHF due to coronary artery disease. For this reason, these agents,with the exception of digoxin, are only used for a short period.

A. Digitalis glycosides

- Come from the digitalis (foxglove) plant.
- Increase the contractility of the heart muscle
- Have a low therapeutic index,
- The most widely used agent is digoxin.
- Digitoxin is seldom used due to its considerable duration of action.

1. Diuretics

1. Thiazide diuretics can be used as initial drug therapy

2. Decreasing blood volume, which ultimately leads to decreased blood pressure.

3. Low-dose diuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and heart failure.

4. Routine serum electrolyte monitoring should be done for all patients receiving diuretics.

Goal of antihypertensive therapy.

1. Reduce cardiovascular and renal morbidity and mortality.

2. Reduces cardiovascular disease.

3. Reduce the systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg.

4. Mild hypertension can sometimes be controlled with monotherapy,but most patients require more than one drug to achieve blood pressure control.

5. Current recommendations are to initiate therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker.

A. Thiazide diuretics

1. Lower blood pressure initially by increasing sodium and water excretion.
2. Decreases extracellular volume, results in a decrease in cardiac output and renal blood flow.
3. With long-term treatment, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a decrease in peripheral resistance.
4. With the exception of metolazone, thiazide diuretics are not effective in patients with inadequate kidney function (Low glomerular filtration rate).
5. Thiazide diuretics can induce hypokalemia, hyperuricemia and, to a lesser extent, hyperglycemia in some patients.

B. Loop diuretics

- Promptly blocks sodium and chloride reabsorption in the kidneys, even in patients with poor renal function or those who have not responded to thiazide diuretics.
- Loop diuretics cause decreased renal vascular resistance and increased renal blood flow.

C. Potassium-sparing diuretics

Amiloride and triamterene (inhibitors of epithelial sodium transport at the late distal and collecting ducts).

Spironolactone and eplerenone (aldosterone receptor antagonists) reduce potassium loss in the urine.

Aldosterone antagonists have the additional benefit of diminishing the cardiac remodeling that occurs in heart failure.

3. Renin Inhibitor

- A selective renin inhibitor, aliskiren, is available for the treatment of hypertension.
- Aliskiren directly inhibits renin and, thus, acts earlier in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs .
- It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides.
- Aliskiren should not be routinely combined with an ACE inhibitor or ARB.
- Aliskiren can cause diarrhea, especially at higher doses, and can also cause cough and angioedema,but probably less often than ACE inhibitors.
- As with ACE inhibitors and ARBs, aliskiren is contraindicated during pregnancy. Aliskiren is metabolized by CYP 3A4 and is subject to many drug interactions.

4. Ca^{+2} Channel Blockers

- Recommended treatment option in hypertensive patients with diabetes or angina.
- High doses should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.

A. Classes of calcium channel blockers

divided into three chemical classes,

1. Diphenylalkylamines: *Verapamil*

Has significant effects on both cardiac and vascular smooth muscle cells.

It is also used to treat angina and supraventricular tachyarrhythmias and to prevent migraine and cluster headaches.

2. Benzothiazepines: *Diltiazem*

Like verapamil, diltiazem affects both cardiac and vascular smooth muscle cells, but it has a less pronounced negative inotropic effect on the heart compared to that of verapamil. Diltiazem has a favorable side effect profile.

3. Dihydropyridines: *Nifedipine* (the prototype),

Eg: *amlodipine, felodipine, isradipine, nicardipine, nisoldipine.*

- All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart.
- They are, therefore, particularly beneficial in treating hypertension.
- The dihydropyridines have the advantage in that they show little interaction with other cardiovascular drugs, such as digoxin or warfarin.

B. Actions

1. Calcium enters muscle cells through special voltage sensitive calcium channels.
2. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium.
3. Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature.
4. This causes vascular smooth muscle to relax, dilating mainly arterioles. Calcium channel blockers do not dilate veins.

C. Therapeutic uses

1. In the management of hypertension

2. They are useful in the treatment of hypertensive patients who also have asthma, diabetes, and/or peripheral vascular disease.

3. All CCBs are useful in the treatment of angina.

4. In addition, diltiazem and verapamil are used in the treatment of atrial fibrillation.

4. α-ADRENOCEPTOR–BLOCKING AGENTS

- Prazosin, doxazosin, and terazosin produce a competitive block of α1-adrenoceptors.
- They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.
- These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

5. α-/β-ADRENOCEPTOR–BLOCKING AGENTS

- Labetalol and carvedilol block α1, β1, and β2 receptors.
- Carvedilol, although an effective antihypertensive, is mainly used in the treatment of heart failure.
- Labetalol is used in the management of gestational hypertension and hypertensive emergencies.

5. CENTRALLY ACTING ADRENERGIC DRUGS

A. Clonidine

1. It acts centrally as an α2 agonist to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery.

2. This leads to reduced total peripheral resistance and decreased blood pressure.

3. Clonidine does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease.

4. Clonidine is absorbed well after oral administration and is excreted by the kidney.
5. Adverse effects include sedation, dry mouth, and constipation.
6. Rebound hypertension occurs following abrupt withdrawal of clonidine. The drug should, therefore, be withdrawn slowly if discontinuation is required.

B. Methyldopa

- Methyldopa is an α2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS.

- The most common side effects of methyldopa are sedation and drowsiness.

- Its use is limited due to adverse effects and the need for multiple daily doses.

- It is mainly used for management of hypertension in pregnancy, where it has a record of safety.

6. VASODILATORS

1. The direct-acting smooth muscle relaxants, such as hydralazine and minoxidil , are not used as primary drugs to treat hypertension.
2. Both agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption.
3. These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals.
4. Vasodilators also increase plasma renin concentration, resulting in sodium and water retention.
5. These undesirable side effects can be blocked by concomitant use of a diuretic and a β-blocker.
6. For example, hydralazine is almost always administered in combination with a β-blocker, such as propranolol, metoprolol, or atenolol (to balance the reflex tachycardia) and a diuretic (to decrease sodium retention).

B. Antiarrhythmic drugs

- It modifies impulse generation and conduction.
- Unfortunately, many of the antiarrhythmic agents are known to have dangerous proarrhythmic actions.
- Inhibition of potassium (K+) channels (class III activity) widens the action potential and can, thus, prolong the QT interval.
- If prolongation is excessive, these drugs increase the risk of developing life-threatening ventricular tachyarrhythmias (torsades de pointes).
- The most common cause of QT prolongation is drug-induced, although other conditions (for example, ischemia and hypokalemia) and genetic profiles may contribute.

CLASS I ANTIARRHYTHMIC DRUGS

1. Act by blocking voltage-sensitive sodium (Na+) channels.
2. The use has declined due to their proarrhythmic effects.
3. Class I drugs bind more rapidly to open sodium channels than to channels that are fully repolarized.
4. Show a greater degree of blockade in tissues that are frequently depolarizing (state dependence).
5. This property enables these drugs to block cells that are discharging at an abnormally high frequency,without interfering with the normal, low-frequency beating of the heart.
6. Subdivided into three groups according to their effect on the duration of the ventricular action potential

B. Class IA antiarrhythmic drugs:

Quinidine,procainamide,and disopyramide

Quinidine is the prototype, they can precipitate arrhythmias

1. Mechanism of action:

Quinidine binds to open and inactivated sodium channels and prevents sodium influx, thus slowing the rapid upstroke during phase 0.

It decreases the slope of phase 4 spontaneous depolarization, inhibits potassium channels, and blocks calcium channels.

Because of these actions, it slows conduction velocity and increases refractoriness.

Quinidine also has mild α-adrenergic blocking and anticholinergic actions.

Procainamide and disopyramide have actions similar to those of quinidine. However, there is less anticholinergic activity associated with procainamide and more with disopyramide.

Neither procainamide nor disopyramide has α-blocking activity.

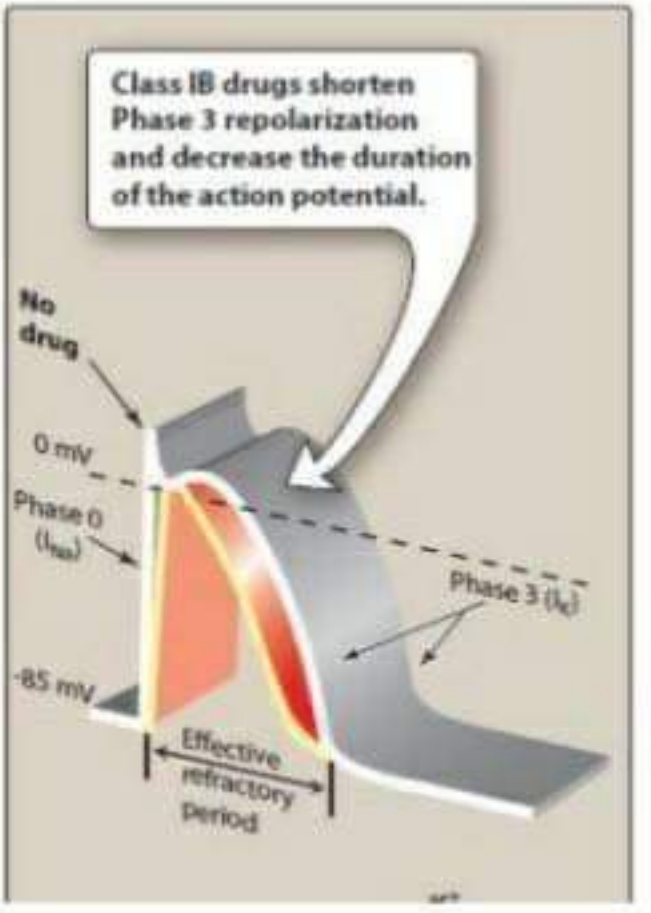
Class IB antiarrhythmic drugs: Lidocaine and mexiletine

The class IB agents rapidly associate and dissociate from sodium channels.

Thus, the actions of class IB agents are manifested when the cardiac cell is depolarized or firing rapidly.

1. Mechanism of action:

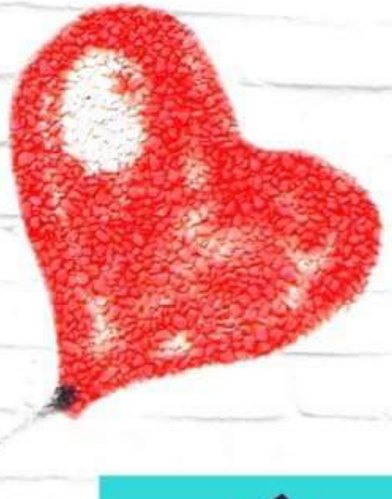
In addition to sodium channel blockade, shorten phase 3 repolarization and decrease the duration of the action potential



VII. OTHER ANTIARRHYTHMIC DRUGS

A. Digoxin

Digoxin inhibits the Na+/K+-ATPase pump, ultimately shortening the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction



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