Pharmacology

Theoretical

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**L.3**

The circulatory system is an organ system that permits blood and lymph circulation

* to transport nutrients (such as amino acids and electrolytes), oxygen, carbon dioxide, hormones, blood cells, etc. to and from cells in the body to nourish it and help to fight diseases,
* stabilize body temperature and pH,
* and to maintain homeostasis.

Type of circulation -------------------------------------

* Pulmonary circulation

- - The pulmonary circulatory system is the portion of the cardiovascular system in which oxygen-depleted blood is pumped away from the heart, via the pulmonary artery, to the lungs and returned, **oxygenated**, to the heart via the pulmonary vein.

* Systemic circulation

- - Systemic circulation is the circulation of the blood to all parts of the body except the lungs. Systemic circulation is the portion of the cardiovascular system which transports oxygenated blood away from the heart through the aorta from the left ventricle where the blood has been previously deposited from pulmonary circulation, to the rest of the body, and returns oxygen-depleted blood back to the heart. Systemic circulation is, distance-wise, much longer than pulmonary circulation, transporting blood to every part of the body

* Coronary circulation

 - The coronary circulatory system provides a blood supply to the myocardium (the heart muscle).

It arises from the aorta by two coronary arteries, the left and the right, and after nourishing the myocardium blood returns through the coronary veins into the coronary sinus and from this one into the right atrium.

* Cardiovascular disease is the major cause of death in the US (>50% of all deaths)
* Major Cardiovascular Pathologies Requiring Pharmacological Intervention

 -Hypertension

 -Arrhythmia

 -Heart failure

 -Reduced vascular blood flow

* Cardiovascular function based on:
* Cardiac pumping ability
* Pace-making electrical signals
* Force of contraction
* Height of ventricle discharge pressure
* Integrity of vasculature
* Presence of blockage
* Muscular tone/structural integrity
* Pressure drop needed to move blood to and through capillary beds
* Blood volume/composition
* Water, electrolyte, iron balances
* Lipid and protein composition
* **Digitalis
( CARDIAC GLYCOSIDES )**
* The cardiac glycosides are often called digitalis or digitalis glycosides, because most of the drugs come from the digitalis (foxglove) plant.
* They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are widely used in treating **HF**. ( heart failure )
* The cardiac glycosides influence the sodium and calcium ion flows in the cardiac muscle, thereby increasing contraction of the atrial and ventricular myocardium (positive inotropic action).
* The digitalis glycosides show only a small difference between a therapeutically effective dose and doses that are toxic or even **fatal**. Therefore, the drugs have a **low** therapeutic index.
* The most widely used agent is digoxin

***Mechanism of action --------------------------------------***

1. Digoxin binds to and inhibits Na/K ATPase.
2. Inhibition of Na/K ATPase **increases** intracellular concentration of Na + ions .
3. Increased intracellular Na + **decreases** the Na + /Ca + + exchanger and allows intracellular Ca + + concentrations to **increase**
4. Increased intracellular Ca + + **increases** the formation of ***actinomyosin*** and **increases** the force of myocardial contractions.

***Therapeutic uses: ------------------------------------***

* The main use of digoxin is the treatment of **CHF**,( chronic heart failure ) to increase the force of contractions.
* Pharmacokinetics
* All digitalis glycosides possess the same pharmacologic actions, but they vary in potency and pharmacokinetics.
* **Digoxin** is very potent, with a narrow margin of safety and long half-life of around 36 hours.
* Digoxin is mainly eliminated intact by the kidney, requiring dose adjustment based on creatinine clearance.
* Digoxin has a large volume of distribution, because it accumulates in muscle.
* A loading dose regimen is employed when acute digitalization is needed.
* **Digitoxin** has a much longer half-life and is extensively metabolized by the liver before excretion in the feces, and patients with hepatic disease may require decreased doses.

Adverse effects: --------------------------------------

* Digitalis toxicity is one of the most commonly encountered adverse drug reactions.
* Side effects often can be managed by discontinuing cardiac glycoside therapy.
* Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs and the use of antibodies to digoxin (**digoxin immune Fab**), which bind and inactivate the drug.
* Types of adverse effects include:
1. Cardiac effects: The common cardiac side effect is arrhythmia, characterized by slowing of atrioventricular conduction associated with atrial arrhythmias. A decrease in intracellular potassium is the primary predisposing factor in these effects.
2. Gastrointestinal effects: Anorexia, nausea, and vomiting are commonly encountered adverse effects.
3. Central nervous system effects: These include headache, fatigue, confusion, blurred vision, alteration of color perception, and halos on dark objects.

Drug Interactions --------------------------------------

* Antacids, laxatives, and cholestyramine can decrease the absorption of digoxin from the GI tract.
* The antiarrhythmic drug quinidine increases digoxin plasma levels. Reduction in digoxin dosage is usually required when these two drugs are used together.
* The calcium channel blockers verapamil and diltiazem and any of the beta-blockers decrease heart rate and force of contraction. These drugs may depress cardiac function and precipitate CHF; this can counteract the therapeutic effectiveness of digoxin.
* Diuretics (thiazides and loop diuretics) cause loss of potassium; hypokalemia can increase digoxin toxicity.

Dose ---------------------------------------------

* Chronic Congestive Heart Failure

 Dose: 0.125 mg po daily