DIGITALIS TOXICITY

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- **Cardioactive Steroids (CAS), or cardiac glycosides, developed their name from the strong cardiac effect on the heart.**
- **The most common pharmaceutical product is digoxin. Other preparations available internationally include digitoxin, ouabain, lanatoside C, deslanoside, and gitaline.**

DIGITALIS TOXICITY

- **Digitalis glycosides are life-saving drugs when they are used in therapeutic doses in the treatment of congestive heart failure, and for management of certain supraventricular rhythm disturbances.**

DIGITALIS TOXICITY

- **Digitalis is usefulness in protecting the ventricles during certain atrial arrhythmias:**
- **It increases the effective refractory period of atrial and ventricular cells.**
- **It also prolongs phase 3 of the cardiac action potential and increases the refractory period of the atrioventricular (AV) node and the Purkinje system.**

DIGITALIS TOXICITY

- **Digoxin is one of the most widely prescribed drugs. Other digitalis preparations are less commonly used.**
- **Prospective studies report that a digitalis glycoside is used by about 15% of all hospitalized persons.**
- **It is also estimated that 20% to 30% of patients taking a digitalis preparation will experience toxicity because the drugs have an extremely narrow therapeutic index.**

DIGITALIS TOXICITY

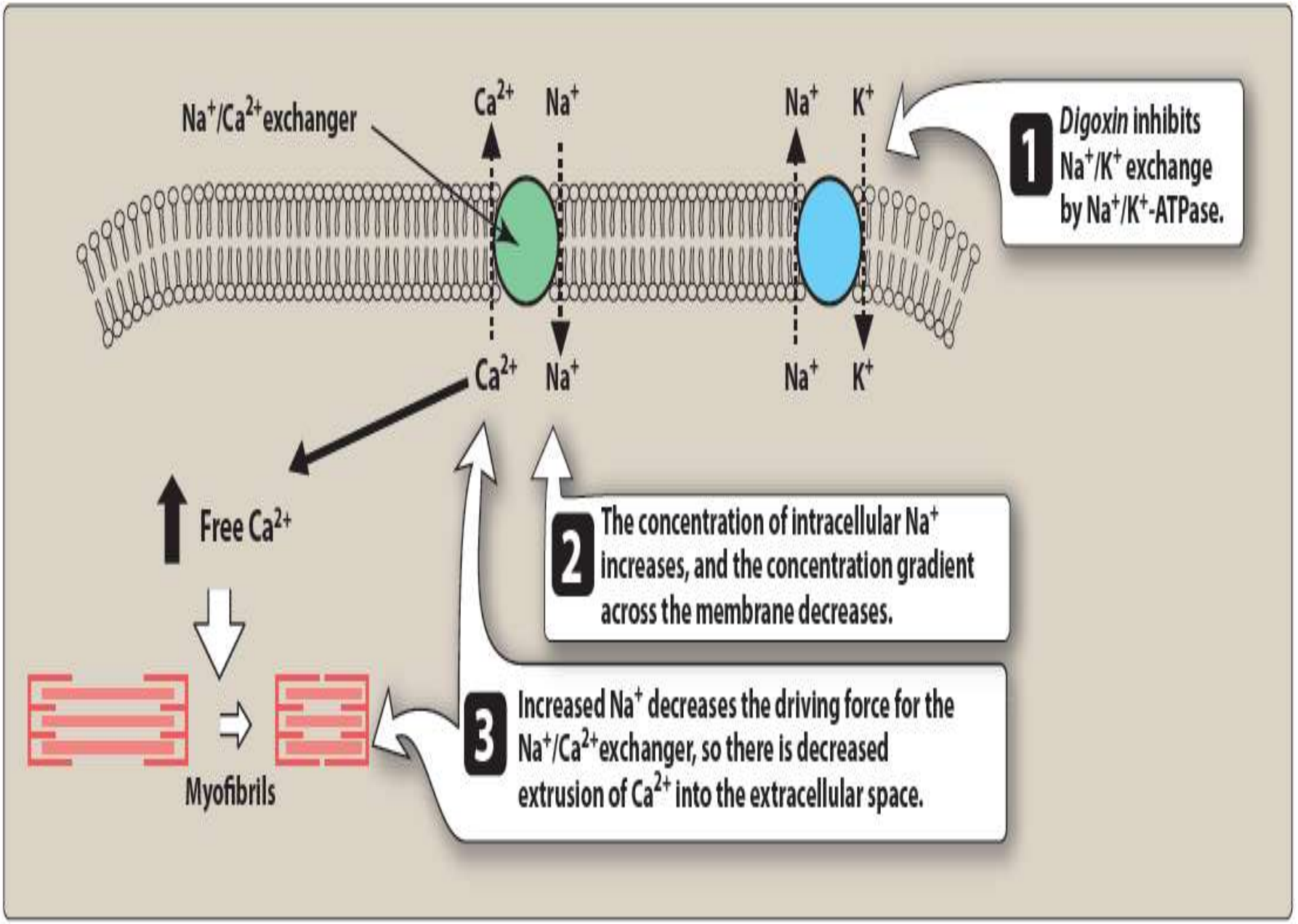
- **The serum concentration of digoxin for therapeutic activity is in the normal range of 1.2 to 1.7 ng/mL.**
- **Concentrations that cause clinically significant toxicity are usually only 2 to 3 times greater . The mortality rate with toxic doses is reported to be as great as 25%.**
- **With increased medical awareness of the problem and availability of sensitive tests for determining serum concentrations, the incidence of poisoning may decrease in the future. Also, with use of the specific antidote (digoxin immune Fab) for treating toxicity, the mortality rate may also improve.**

Causes of digitalis toxicity

- **Excessive intake is a common cause of poisoning. Accidental overdose usually occurs in children. Suicide with digitalis is not common in the United States, although it is more prevalent in other countries.**
- **Concurrent administration of a diuretic that induces potassium loss is reported to be the most frequent cause of toxicity.**
- **Variability in bioavailability of digoxin tablets was a common cause of toxicity until recently.**

Mechanism of Action:

- **Inhibit active transport of Na+ and K+ across the cell membrane during repolarization by binding to a specific site on the extracellular face of the alpha-subunit of the membrane Na-K-ATPase**


Na+/Ca2+exchanger
Ca2+
Na+
Na+
K+
1 Digoxin inhibits Na+/K+ exchange by Na+/K+-ATPase.
Ca2+
Na+
Na+
K+
Free Ca2+
2 The concentration of intracellular Na+ increases, and the concentration gradient across the membrane decreases.
3 Increased Na+ decreases the driving force for the Na+/Ca2+exchanger, so there is decreased extrusion of Ca2+ into the extracellular space.
Myofibrils

Pharmacokinetics

- **The half-life of digoxin is about 1.5 days. Renal excretion is the major route of elimination.**
- **Digitoxin is the least polar of the digitalis glycosides. It, therefore, binds readily with serum proteins and is excreted slowly, with a half-life of 4 to 6 days.**
- **Digoxin has a large volume of distribution, which limits the usefulness of dialysis.**

Digoxin drug interaction

- **Digitalis intoxication is influenced by the presence of other drugs. Combined use of quinidine and digoxin can result in a two-fold increase in serum digoxin concentration. The total body clearance and volume of distribution are reduced; the half-life is not prolonged. Though the exact mechanism of this interaction is not fully known, displacement of digoxin from tissue-binding sites appears to be a likely mechanism. A similar interaction has also been demonstrated with verapamil.**

Mechanism of Toxicity

- **Toxicity is believed to result from an extension of pharmacologic actions.**
- **A toxic dose of digitalis interferes with transport of Na and Ca. The glycosides bind with high affinity to an inhibitory site on the portion of the Na K-ATPase structure that faces the outside of the cell. Consequently, Na and K transport are blocked as long as the drug molecule remains in place. Since K transport back into cells is blocked, its concentration in the extracellular fluid increases. This is why serum concentration is a good indication of the extent of digitalis poisoning.**

- **The changes in Na fluxes across cardiac cell membranes result in disturbed impulse conduction. Accumulation of Ca intracellular produces a positive inotropic action.**
- **An overdose of digitalis causes a reduction in resting membrane potentials, and cardiac pacemaker cells cannot function properly. The outcome is a systole with complete loss of all cardiac function.**

Factors that increase the risk of toxicity to digitalis glycosides:

- **Concurrent administration of a diuretic that induces potassium loss is reported to be the most frequent cause of toxicity.**
- **Individuals with Eubacterium lentum in their colon may require larger doses of digitalis to achieve the desired therapeutic serum concentrations. This microorganism reduces the lactone ring of digitalis.**
- **Digitalis blood concentrations may become toxic when these patients receive antibiotics, such as tetracycline or erythromycin, which eradicate the organism.**

- **Since 60-80% of digoxin is excreted through the kidneys, decreased renal excretion would result in accumulation of digoxin & toxicity.**
- **Hypokalemia results in increased digoxin binding increasing its therapeutic and toxic effects.**
- **Hypothyroidism: may reduce the requirements for digoxin due to decreased volume of distribution and plasma clearance of the drug. Therapy with digoxin should be initiated at lower dosages in patients with hypothyroidism to avoid toxicity.**
- **Hypercalcemia: Digoxin enhances Ca+2 absorption into cardiac myocytes, which is one of the ways it increases inotropy. This can also lead to Ca+2 overload and increased susceptibility to digitalis-induced arrhythmias.**
- **Hypomagnesemia: Can sensitize the heart to digitalis-induced arrhythmias (includes any arrhythmia except supraventricular tachydysrhythmias).**

Characteristics of poisoning:

- **Early manifestations of intoxication that occur in approximately 50% of all cases generally involve the gastrointestinal tract. Anorexia, nausea, vomiting, & abdominal pain are common. Nausea & vomiting occur from direct drug action on the chemoreceptortriggerzone (CTZ).**
- **Blurred vision, loss of visual acuity, & green yellow halos have been described as early-appearing symptoms.**
- **CNS effects include a variety of neuropsychiatric disturbances such as confusion, drowsiness, headache, hallucinations**
- **Cardiac effects include bradycardia, heart block, several types of arrhythmias**

Diagnosis

- **Studies in patients with possible digitalis toxicity include the following:**
  - **Electrolytes (In acute toxicity, hyperkalemia is common)**
  - **Renal function studies**
  - **ECG (Digoxin toxicity may cause almost any dysrhythmia)**
  - **Serum digoxin level:**

Digoxin levels in the poisoned patient:

- **Obtaining an immediate digoxin level in an acutely poisoned patient will not reflect the peak serum level as the distribution phase of digoxin is long. An initial 4-6 hour post-ingestion level is appropriate.**

- **Unbound digoxin: Useful following administration of digoxin-specific Fab fragments**

- **Total digoxin (bound & unbound): Serum concentrations predict cardiac concentrations. Also Fab fragments of digoxin-specific antibodies will cause a rise in total digoxin levels (as Fab bound digoxin is also being measured)**

Management of poisoning:

- **Management involves:**
- **removal of ingested drug,**
- **maintenance of a normal potassium concentration,**
- **reversal of arrhythmias,**
- **and increased removal of unabsorbed drug.**
- **More recently, it may include the use of a specific antidote, digoxin immune Fab.**

- **Gastric lavage should be performed to remove the unabsorbed drug, although vomiting may already have accomplished this.**
- **Repeated administration of activated charcoal or cholestyramine is recommended for acute overdose. Activated charcoal can adsorb digoxin in the gut.**
- **Enhanced elimination (dialysis, hemoperfusion) does not effectively remove digoxin due to large volume of distribution and relatively high protein binding.**

- **Hyperkalemia (5.5-13.5 mEq/L) is caused by acute digitalis toxicity, while hypokalemia is more common with chronic digitalis use.**
- **Hyperkalemia may require treatment with insulin plus glucose, &sodium bicarbonate.**
- **If hypokalemia is encountered with tachy- or bradyarrhythmias, continuous potassium replacement alone may be sufficient.**

- **For atrial & ventricular arrhythmias that do not respond to potassium therapy, the treatment of choice includes phenytoin & lidocaine. An advantage to using these drugs is that they depress ventricular automaticity without slowing AV nodal conduction, as seen with quinidine and procainamide. Additionally, phenytoin increases AV nodal conduction and directly reverses the toxic action of digitalis at the AV node without interfering with its inotropic action.**

- **Potassium administration in a person with digitalis induced hyperkalemia can result in heart block.**
- **If digitalis has produced (AV) block, atropine is given to produce vagolytic effect to increase the heart rate &AV conduction.**
- **Catecholamines are contraindicated for treating bradyarrhythmias resulting from digitalis toxicity. They can increase the risk of precipitating more serious ectopic arrhythmias.**

- **β-blockers, such as propranolol, are useful to suppress supraventricular & ventricular arrhythmias but may depress the sinoatrial (SA) node & AV conduction especially in a patient with an already failing heart, that limiting their usefulness.**
- **Because digoxin has a large volume of distribution, hemodialysis is not a successful method to enhance elimination of digoxin.**

Digoxin Immune Fab (Digibind):

- **Digoxin immune Fab is used as an antidote reserved for life-threatening overdoses. Indications of such toxicity include:**
- **• ingestion of more than 10 mg of digoxin by healthy adults or 4 mg by children,**
- **• Steady-state serum concentrations greater than 10 ng/mL; or**
- **• if blood potassium concentration exceeds 5 mEq/L.**

Digoxin immune fab (Digibind): Mechanism of action

- **Binds to digoxin molecules, reducing free digoxin levels which results in a shift in the equilibrium away from receptor binding. Fab-digoxin complexes are cleared by the kidney and mononuclear phagocyte system.**

Digoxin immune fab (Digibind): Dosing

- Dosage of digibind can be calculated according to the amount of digoxin or digitoxin in the patient's body. When steady-state serum concentrations of digoxin or digitoxin is known, the total body load can be estimated as shown below:
- **Body load(mg)= (SDC) (mean Vd) (wt in Kg) 1000**
- SDC is the serum digitalis concentration in ng/mL. Vd: volume of distribution Vd of digoxin = 5.6 L/kg Vd of digitoxin = 0.56 L/kg

- **Each vial of antidote contains 40 mg of digibind. This will bind 0.6 mg digoxin or digitoxin. The total number of vials needed can be obtained by dividing the total body load of drug in mg, by 0.6 mg/vial.**

Digoxin immune fab: warnings

- **Monitor potassium level frequently as a rapid drop in serum potassium may occur following digoxin immune fab administration**
- **Patients who require digoxin's inotropic action may deteriorate secondary to the withdrawal of digoxin's inotropic action by digoxin immune fab. Additional inotropic support may be required for these patients (e.g, dopamine, dobutamine or vasodilators). Re-digitalization may need to be postponed until digoxin immune fab has been cleared (several days to more than a week of impaired renal function)**
- **Patients with allergies to sheep protein or prior treatment with ovine antibodies or Fab are at risk for an anaphylactic reaction.**

Adverse effects:

1. **Worsening of congestive heart failure**
2. **A rapid shift of potassium back into the cell can occur when digoxin toxicity is reversed by digoxin immune fab. So serum potassium should be followed closely and supplementation should be given cautiously.**
3. **Worsening of atrial fibrillation.**