Cardiac Glycosides: Digoxin, Mechanism of Action, Dosage and Toxicity

Digoxin is a **cardiac glycoside** , a class of naturally derived compounds originally extracted from the **foxglove plant (*Digitalis purpurea*)** . It is primarily used in the **management of atrial arrhythmias** and **heart failure** due to its **positive inotropic** and **vagomimetic effects** .

Examples of Cardiac Glycosides

- **Digoxin** – the most commonly used in clinical practice
- **Digitoxin**
- **Ouabain**

High-Yield Fact : All cardiac glycosides share a similar mechanism of action - inhibition of the **Na?/K?-ATPase pump** , which indirectly increases intracellular calcium to enhance myocardial contractility.

Mechanism of Action

In Heart Failure (Positive Inotropic Effect)

1. **Na?/K?-ATPase Inhibition** : Digoxin inhibits the sodium-potassium pump in cardiac myocytes.
2. **? Intracellular Na?** : This reduces the sodium gradient across the sarcolemma.
3. **? Na?/Ca²? Exchange** : Less sodium entry = less calcium extrusion.
4. **? Intracellular Ca²?** : Calcium is sequestered in the sarcoplasmic reticulum and released during contraction.
5. **? Actin-Myosin Interaction** : Enhanced cardiac contractility (positive inotropy).

In Atrial Arrhythmias (Negative Chronotropic and Dromotropic Effects)

- **Vagal Stimulation** : Digoxin enhances parasympathetic (vagal) tone.
- **? SA Node Firing** : Reduces heart rate (negative chronotropy).
- **? AV Node Conduction** : Prevents rapid ventricular rates in atrial fibrillation/flutter (negative dromotropy).

Used mainly to control **ventricular rate** in atrial fibrillation/flutter, especially in patients with concurrent heart failure.

Pharmacokinetics

- **Routes of Administration** : Oral and intravenous (IV)
- **Onset** :

    - Oral: ~2 hours
    - IV: ~30 minutes
- **Half-life** : ~36–48 hours (prolonged in renal impairment)
- **Volume of Distribution** : High (binds extensively to tissues)
- **Metabolism & Clearance** : Primarily **renal excretion**

Digitalization (Loading Dose)

Due to slow onset and long half-life, loading doses are used to rapidly achieve therapeutic plasma concentrations.

Therapeutic Range and Monitoring

- **Therapeutic Plasma Concentration** : 0.5 – 1.5 ng/mL
- **Toxic Level** : > 2.0 ng/mL

  Always monitor renal function and serum electrolytes (K?, Mg^{2}?, Ca^{2}?) in patients on digoxin to avoid toxicity.

Toxicity (Digitalis Toxicity)

Risk Factors

- Renal impairment
- Hypokalemia, hypomagnesemia
- Drug interactions
- Elderly patients

Early Signs

- Anorexia
- Nausea, vomiting
- Fatigue
- Visual disturbances (e.g., yellow-green halos)

ECG Changes

- Premature ventricular contractions (PVCs)
- AV block
- Bradycardia
- ST depression with scooped appearance (“digitalis effect”)

Severe Toxicity

- Life-threatening arrhythmias (e.g., ventricular tachycardia/fibrillation)
- Confusion, delirium

Management

- **Stop Digoxin**
- **Correct electrolytes** (especially potassium)
- **Administer Digoxin-specific antibody fragments (Digibind or DigiFab)**
- **Class IB antiarrhythmics** (e.g., lidocaine or phenytoin) in case of ventricular arrhythmias

Digibind is used in **severe toxicity** , especially when arrhythmias are unresponsive to supportive therapy.

Drug Interactions

Drug/Class	Effect
Amiodarone	? Digoxin levels (? clearance)
Verapamil, Diltiazem	? Plasma levels (? renal excretion)
Quinidine, Propafenone	Compete for binding sites, ? Digoxin
Diuretics (loop, thiazide)	Cause **hypokalemia** , ? toxicity risk
NSAIDs	Reduce renal blood flow, ? clearance
Tolvaptan	Alters Na? balance, ? Digoxin effect

Clinical Uses of Digoxin

Condition	Role of Digoxin
Atrial Fibrillation/Flutter	Rate control (esp. in HF)
Chronic Heart Failure	Enhances contractility in reduced ejection fraction HF (HFrEF)
Paroxysmal Supraventricular Tachycardia (PSVT)	Less commonly used, vagomimetic effect helps AV nodal suppression

Note : Not typically used in **acute decompensated heart failure** due to delayed onset of action.

Contraindications

- Ventricular fibrillation
- AV block without pacemaker
- Acute myocardial infarction (caution)
- Hypokalemia, hypomagnesemia (predispose to toxicity)