

## Digoxin

**Introduction:** Digoxin is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium.

**Mechanism of action:** Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system.

### Pharmacology:

**Absorption:** Absorption of digoxin has been demonstrated to be 60% to 80% complete compared to an identical intravenous dose of digoxin (absolute bioavailability) or Digoxin

**Distribution:** Following drug administration, a 6-to 8-hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation.

**Metabolism:** Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3  $\beta$ -digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

**Excretion:** Elimination of digoxin follows first-order kinetics. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow.

### Indications:

**Heart Failure:** Digoxin is indicated for the treatment of mild to moderate heart failure. Digoxin increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality.

**Atrial Fibrillation:** Digoxin is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

### Dosage:

**Heart Failure: Adults:** Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same end point in terms of total amount of digoxin accumulated in the body.

- If rapid digitalization is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.
- More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately five half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

**Maintenance Dosing:** The doses of digoxin used in controlled trials in patients with heart failure have ranged from 125 to 500 mcg (0.125 to 0.5 mg) once daily.

**Infants and Children:** In general, divided daily dosing is recommended for infants and young children (under age 10). In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area. Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults.

**Atrial Fibrillation:** Peak digoxin body stores larger than the 8 to 12 mcg/kg required for most patients with heart failure and normal sinus rhythm have been used for control of ventricular rate in patients with atrial fibrillation. Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects.

**Side effects:** Common side effects include nausea, vomiting, headache, dizziness, skin rash, and mental changes. Serious side effects associated with digoxin include heart block, rapid heartbeat, and slow heart rate. Digoxin has also been associated with visual disturbance (blurred or yellow vision), abdominal pain, and breast enlargement. Patients with low blood potassium levels can develop digoxin toxicity even when digoxin levels are not considered elevated. Similarly, high calcium and low magnesium blood levels can increase digoxin toxicity and produce serious disturbances in heart rhythm.

**Precautions:**

**Use in Patients with Impaired Renal Function:** Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function. If appropriate care is not taken to reduce the dose of

digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

**Use in Patients with Electrolyte Disorders:** In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2 ng/mL, because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

**Use in Thyroid Disorders and Hypermetabolic States:** Hypothyroidism may reduce the requirements for digoxin. heart failure and/or atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (e.g., hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is used.

**Use in Patients with Acute Myocardial Infarction:** Digoxin should be used with caution in patients with acute myocardial infarction. The use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischemia.

**Pregnancy:** Digoxin should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** Caution should be exercised when digoxin is administered to a nursing woman.

**Pediatric Use:** Premature and immature infants are particularly sensitive to the effects of digoxin. Digoxin glycosides can cause poisoning in children due to accidental ingestion.

**Geriatric Use:** Drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function.

**Contraindications:** Digoxin glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin.

**How supplied: Customized as per request.**