Centoxin®

Digoxin

Description: Digoxin is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having common specific effects on the myocardium and is used in heart failure and atrial fibrillation.

Mode of action: Digoxin binds to a site on the extracellular aspect of the a-subunit of the Na+/K+ ATPase pump in the membranes of heart cells (myocytes) and decreases its function. Inhibition of the Na+/K+ pump leads to increased intracellular Na+ levels, which in turn slows down the extrusion of Ca2+ by the sodium-calcium this leads to increased contractility of the heart.

Pharmacokinetics: Distribution: Following drug administration, a 6- to 8-hour tissue distribution phase is observed. Approximately 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates with lean (i.e., ideal) body weight, not total body weight.
Excretion: The serum half-life of digoxin in children is reported to be 18 to 36 hours, and in adults it is typically 36 to 48 hours. The half-life in anuric patients is prolonged to 3.5 to 5 days.
Metabolism: Only a small percentage of digoxin is metabolized. The end metabolites, which include 3- igoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to form via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent on cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.
Absorbtion: Following oral administration, peak serum concentrations of digoxin occur at 30 to 90 minutes. In children and in adult volunteers, absolute bioavailability of digoxin from the solution formulation is 70 to 85%, similar to that seen (in adults) with standard tablets (60 to 80%). When the solution is taken after meals, the peak serum concentrations increase by 20% and the total amount of digoxin absorbed increases by 43%.

Composition: Centoxin® 0.25 mg Tablet: Each tablet contains digoxin USP 0.25 mg.
Centoxin® 60 ml Solution: Each ml contains digoxin USP 50 mcg (0.05 mg).

Indications: Digoxin is indicated for the treatment of chronic heart failure. Digoxin is also indicated in the management of atrial fibrillation.

Dosage and administration: Recommended dosage of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications.

Rapid digitalization with a loading dose:
Tablet: If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then base calculation of the maintenance dose upon the amount actually given.
A single initial dose of 500 to 750 mcg (0.5 to 0.75 mg) of digoxin tablets usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2 to 6 hours. Give additional doses of 125 to 375 mcg (0.125 to 0.375 mg) cautiously at 6 to 8 hour intervals until clinical evidence of an adequate effect is noted. The usual amount of digoxin tablets that a 70 kg patient requires to achieve 8 to 12 mcg/kg peak body stores is 750 to 1,250 mcg (0.75 to 1.25 mg)

Solution: Digitalizing and daily maintenance doses for each age group are given below and should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. These recommendations assume the presence of healthy renal function.

Usual Digitalizing and Maintenance Dosages for Digoxin Pediatric Solution in Children with Healthy Renal Function Based on Lean Body Weight

Age	Oral digitalizing[a] dose (mcg/kg)	Daily maintenance dose[b] (mcg/kg)
Premature	20 to 30	20% to 30% of oral digitalizing dose[c]
Full-term	25 to 35	25% to 35% of oral digitalizing dose[c]
1 to 24 months	35 to 60	
2 to 5 years	30 to 40	
5 to 10 years	20 to 35	
Over 10 years	10 to 15	

[a] IV digitalizing doses are 80% of oral digitalizing doses.
[b] Divided daily dosing is recommended for children younger than 10 years age.
[c] Projected or actual digitalizing dose providing clinical response.
In children with renal disease, carefully titrate digoxin dosing based upon desired clinical response.
Maintenance dose: The doses of digoxin tablets used in controlled trials in patients with heart failure have ranged from 125 to 500 mcg (0.125 to 0.5 mg) once daily. In these studies, the digoxin dose has been generally titrated according to the patient's age, lean body weight and renal function. Therapy is generally initiated at a dosage of 250 mcg (0.25 mg) once daily in patients younger than 70 years of age with good renal function, at a dosage of 125 mcg (0.125 mg) once daily in patients older than 70 years of age or with impaired renal function and at a dosage of 62.5 mcg (0.0625 mg) once daily in patients with marked renal impairment. Doses may be increased every 2 weeks according to clinical response.
[a] Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. For adults, if only serum creatinine concentrations (Scr) are available, a Ccr (Corrected to 70 kg body weight) may be estimated in men as (140 – age)/Scr. For women multiply this result by 0.85.

Note: This equation cannot be used for estimating in infants or children.
[b] If no loading dose administration.
[c] 62.5 mcg = 0.0625 mg.

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. Titrate doses of Digoxin

Usual Daily Maintenance Dose Requirements (mcg) of Digoxin for Estimated Peak Body Stores of 10 mcg/kg

Corrected Ccr (ml/min per 70 kg)[a]	Lean Body Weight							No. of Days Before Steady State Achieved[b]
	kg	50	60	70	80	90	100	
	lb	110	132	154	176	198	220	
0		62.5[c]	125	125	125	187.5	187.5	22
10		125	125	125	187.5	187.5	187.5	19
20		125	125	187.5	187.5	187.5	250	16
30		125	187.5	187.5	187.5	250	250	14
40		125	187.5	187.5	250	250	250	13
50		187.5	187.5	250	250	250	250	12
60		187.5	187.5	250	250	250	375	11
70		187.5	250	250	250	250	375	10
80		187.5	250	250	250	375	375	9
90		187.5	250	250	250	375	500	8
100		250	250	250	375	375	500	7

used for the treatment of chronic atrial fibrillation to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects.

Contraindications: Digoxin is 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.

Side effects: These are principally associated with overdosage but may occur from temporary high serum concentration due to rapid absorption. They include anorexia, nausea, vomiting, diarrhoea, weakness, dizziness, headache, skin rashes, gynaecomastia, atrial tachycardia.

Use in pregnancy and lactation: The use of digoxin in pregnancy is not contraindicated. Use should be considered only when the expected clinical benefit of the treatment to the mother outweighs any possible risk to the developing foetus. Although digoxin is excreted in breast milk, the quantities are minute and breast feeding is not contraindicated.

Precautions: Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin. Hypokalemia or hypomagnesemia sensitizes the myocardium to digoxin. Hypothyroidism may require low dose and hyperthyroidism and malabsorption may require larger dose. It may be desirable to reduce the dose of digoxin for 1 to 2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of ventricular arrhythmias.

Drug interactions: Potassium-depleting diuretics are a major contributing factor to digoxin toxicity. Calcium, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam, and spironolactone raise the serum digoxin concentration Erythromycin, clarithromycin and tetracycline may increase digoxin absorption. Propantheline and diphenoxylate may increase digoxin absorption. Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine, certain anticancer drugs, and metoclopramide may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations.

Over dosage: Digoxin should be temporarily discontinued until the adverse reaction resolves. Every effort should also be made to correct factors that may contribute to the adverse reaction (such as electrolyte disturbances or concurrent medications). Once the adverse reaction is resolved, therapy with digoxin may be re-instituted, following a careful reassessment of dose. Withdrawal of digoxin may be all that is required to treat the adverse reaction. However, when the primary manifestation of digoxin overdosage is a cardiac arrhythmia, additional therapy may be needed. If heart block occurs, insertion of a temporary cardiac pacemaker may be required.

Storage: Keep out of reach of children. Store in a cool and dry place, protected from light.

Packaging
Centoxin® 0.25 mg Tablet: Each carton contains 10X5 tablets in blister strips.
Centoxin® 60 ml Solution: Each carton contains a bottle having 60 ml solution and a dropper.

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