

DIGOXIN

Robert DiDomenico and Robert L. Page II

In 1785, Sir William Withering published the first accounts of digitalis (dried leaves of the purple foxglove) in cardiovascular medicine.¹ Since that time, digoxin has become well established for use in systolic heart failure (HF) and controlling ventricular response in atrial fibrillation and flutter.^{2,3}

Digoxin’s mechanism of action is multifaceted. Historically, digoxin’s positive inotropic effects were thought to result primarily from inhibition of the sodium-potassium ATPase pump. This inhibition reduces the transmembrane sodium gradient, which indirectly inhibits the sodium-calcium exchanger and thereby allows calcium to accumulate in myocytes. As intracellular calcium increases, so does the heart’s contractile force. Over the past decade, digoxin has also been noted to alter neurohormonal systems, particularly through the autonomic nervous system. These autonomic effects include a vagomimetic action that is responsible for digoxin’s sinoatrial and atrioventricular (AV) nodal effects and an increase in baroreceptor sensitization, which enhances afferent inhibitory activity and diminishes sympathetic nervous system and renin-angiotensin system activities.⁴

Unfortunately, digoxin has a fairly narrow therapeutic range and warrants reasonably cautious dosage determination. It should generally be avoided in patients with sinus node disease, second- or third-degree AV block, accessory AV pathways (Wolff-Parkinson-White syndrome), cardiac amyloidosis, and hypertrophic cardiomyopathy.⁵

USUAL DOSAGE RANGE IN ABSENCE OF CLEARANCE-ALTERING FACTORS

The loading and maintenance dosage ranges shown in **Table 13-1** are based on lean or ideal body weight in patients with normal renal function for their age and on administration of the tablet or elixir form of digoxin.^{6,7}

TABLE 13-1. LOADING AND MAINTENANCE DOSES^{6,7,11}

Dosage Form	Loading Dose ^a	Maintenance Dose ^a
IV		
Premature neonates (<4 wk)	15–25 mcg/kg	5–10 mcg/kg/day ^b
Full-term neonates	20–30 mcg/kg	8–10 mcg/kg/day ^b
Oral (elixir) ^c		
Infants (<2 yr)	38–63 mcg/kg	13–15 mcg/kg/day ^b
Children (2–10 yr)	25–44 mcg/kg	10–13 mcg/kg/day ^b
Children (>10 yr)	10–15 mcg/kg	4–13 mcg/kg/day ^d
Oral (tablets)		
Adults	10–15 mcg/kg ^e	62.5–250 mcg/day ^d

IV = intravenous.

^aBased on ideal body weight (IBW) or lean body weight (LBW).

^bDivided into two doses given every 12 hr for children <10 yr.

^cDoses adjusted according to dosage form bioavailability.

^dAdministered once daily except 62.5 mcg/day dose, which may be given as 125 mcg every other day.

^eThree divided doses.

For adults with normal renal function, the usual approach is administration of a total loading dose of approximately 10 mcg/kg based on ideal body weight, generally 0.75–1.5 mg for most patients.^{8,9} Approximately 50% of the total load is given as the first dose (e.g., 0.5 mg) followed by 25% (e.g., 0.25 mg) administered at 6- to 8-hr intervals orally or IV after the first dose is given. Whether given IV or orally, the digoxin load is usually carried out over 24 hr with three to four divided doses. This approach is based on the onset of digoxin's effect (and primarily onset of negative side effects that can be averted by holding the remainder of the load if necessary), which is determined by the rate of distribution to the site of action. For an IV dose, 1–4 hr is required to achieve the full effect from the dose while 2–6 hr is required for an oral dose.⁷ Larger loading doses and more aggressive dosing regimens may be required to control the ventricular rate in atrial fibrillation and flutter.^{2,10} In patients with HF, digoxin loading is not recommended.³ Once completed, the load is followed by a daily maintenance dose, typically 0.125–0.25 mg/day.^{6,7,11}

For patients with impaired renal function (creatinine clearance [CrCl] \leq 20 mL/min), a smaller loading dose (e.g., 0.5 mg), given either IV or orally (two 0.25-mg doses 6 hr apart), may be considered followed by 0.0625–0.125 mg/day.^{6,7,11}

Maintenance doses should be based on the condition being treated, renal function, patient response, and digoxin concentrations. When used for the management of systolic dysfunction in patients with normal sinus rhythm, digoxin is typically not loaded, but rather initiated at a daily maintenance dose of 0.125 mg or 0.25 mg, depending on renal function. This approach decreases the risk of overshooting digoxin concentrations. **Table 13-2** lists proposed maintenance dosages and interval adjustments based on CrCl.

Digoxin is available in a number of different dosage forms, making it convenient to switch forms when necessitated by changing patient condition. Dosage forms are shown in **Table 13-3**.

It is important to note that the bioavailability of digoxin differs among the dosage forms (**Table 13-4**), and when patients are changed from one route of administration or dosage form to another, differences in bioavailability should be considered.

TABLE 13-2. CRCL-BASED MAINTENANCE DOSAGES AND INTERVAL ADJUSTMENTS¹²

CrCl	Percent of Normal Recommended Maintenance Dose	Interval
>50 mL/min	100%	24 hr
10–50 mL/min	25% to 75%	24–36 hr ^a
<10 mL/min	10% to 25%	48 hr

^aThe 36-hr interval is not recommended, because of complicated dosing schedules.

TABLE 13-3. DOSAGE FORM AVAILABILITY⁷

Dosage Form	Product
IV	
0.25 mg/mL	Digoxin injection, Lanoxin injection
0.1 mg/mL	Digoxin pediatric injection, Lanoxin injection pediatric
Oral capsules (liquid filled)	
0.05, 0.1, and 0.2 mg	Lanoxicaps
Oral tablets	
0.125 mg	Digitek
0.0625, 0.125, 0.1875, and 0.25 mg	Lanoxin
Oral elixir	
0.05 mg/mL	Digoxin elixir; Lanoxin elixir pediatric