Digoxin

- Digoxin is the primary cardiac glycoside in clinical use.
- Digoxin is used for the treatment of congestive heart failure (CHF) because of its inotropic effects on the myocardium and for the treatment of atrial fibrillation because of its chronotropic effects on the electrophysiological system of the heart.
- The positive inotropic effect of digoxin is caused by binding to sodium- and potassium activated adenosine triphosphatase, also known as Na,K-ATPase or the sodium pump.
- The chronotropic effects of digoxin are mediated via increased parasympathetic activity and vagal tone.

THERAPEUTIC AND TOXIC CONCENTRATIONS

- When given as oral or intravenous doses, the serum digoxin concentration–time curve follows a two-compartment model and exhibits a long and large distribution phase of 8–12 hours . During the distribution phase, digoxin in the serum is not in equilibrium with digoxin in the tissues, so digoxin serum concentrations should not be measured until the distribution phase is finished. When drug distribution is complete, digoxin serum and tissue concentrations will be proportional to each other so that digoxin serum concentrations reflect concentrations at the site of action.

- digoxin serum concentration is very high but the patient is not exhibiting signs or symptoms of digitalis overdose, clinicians should consider the possibility that the blood sample for the determination of a digoxin serum concentration was obtained during the distribution phase, is too high because digoxin has not had the opportinunity to diffuse out of the bloodstream into the myocardium, and is not reflective of myocardial tissue concentrations.

- ❖ inotropic effects of digoxin are generally achieved at steady-state serum concentrations of 0.5–1 ng/mL. Increasing steady-state serum concentrations to 1.2–1.5 ng/mL may provide some minor, additional inotropic effect.
- ❖ Chronotropic effects usually require higher digoxin steady-state serum concentrations of 0.8–1.5 ng/mL. Additional chronotropic effects may be observed at digoxin steady-state serum concentrations as high as 2 ng/mL.
- ❖ Steady-state digoxin serum concentrations above 2 ng/mL are associated with an increased incidence of adverse drug reactions. At digoxin concentrations of 2.5 ng/mL or above ~50% of all patients will exhibit some form of digoxin toxicity.
- ❖ Most digoxin side effects involve the gastointestinal tract, central nervous system, or cardiovascular system.
  - ▪ Gastrointestinal-related adverse effects include anorexia, nausea, vomiting, diarrhea, abdominal pain, or constipation.
  - ▪ Central nervous system side effects are headache, fatigue, insomnia, confusion, or vertigo.
  - ▪ Cardiac side effects commonly include second or third degree atrioventricular block, atrioventricular dissociation, bradycardia, premature ventricular contractions, or ventricular tachycardia

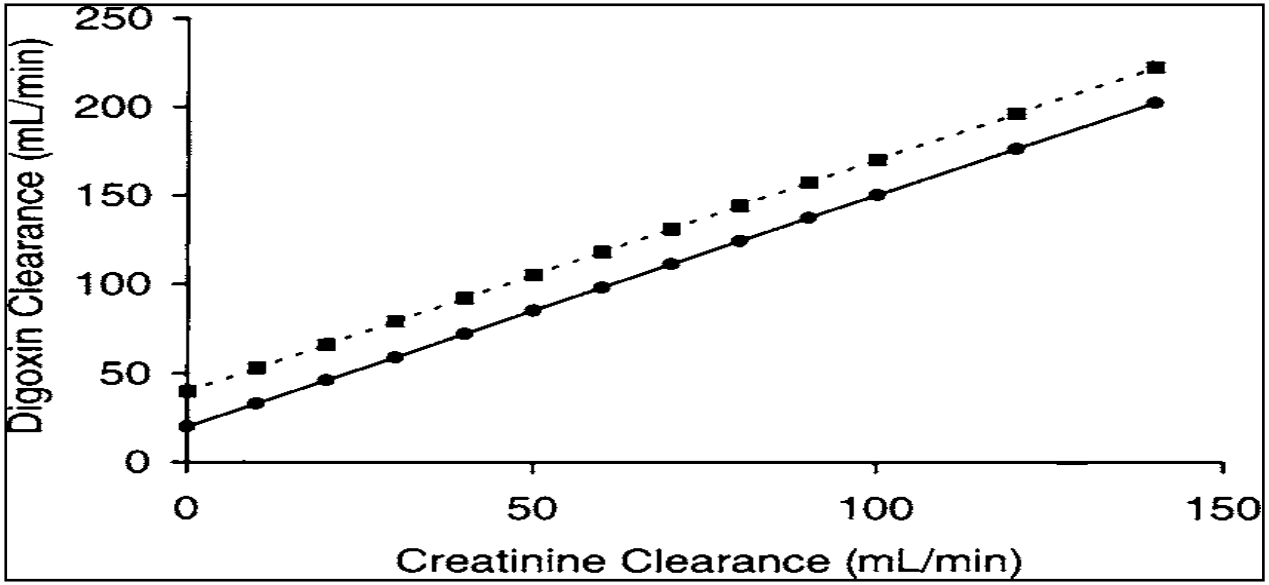
BASIC CLINICAL PHARMACOKINETIC PARAMETERS

- The primary route of digoxin elimination from the body is by the kidney via glomerular filtration and active tubular secretion of unchanged drug (~75%).

The remainder of a digoxin dose (~25%) is removed by hepatic metabolism or biliary excretion. Enterohepatic recirculaton (reabsorption of drug from the gastrointestinal tract after elimination in the bile) of digoxin occurs.

- Digoxin is given as an intravenous injection or orally as a tablet, capsule, or elixir. When given intravenously, doses should be infused over at least 5–10 minutes.
- Average bioavailability constants (F) for the tablet, capsule, and elixir are 0.7, 0.9, and 0.8.
- Plasma protein binding is ~25% for digoxin.
- Usual digoxin doses for adults are 250 μg/d (range: 125–500 μg/d) in patients with good renal function (creatinine clearance ≥80 mL/min) and 125 μg every 2–3 days in patients with renal dysfunction (creatinine clearnace ≤15 mL/min).

The digoxin clearance rate decreases in proportion to creatinine clearance. The equation that estimates digoxin clearance from creatinine clearance is: Cl = 1.303 (CrCl) + ClNR, where Cl is digoxin clearance in mL/min, CrCl is creatinine clearance in mL/min, and ClNR is digoxin clearance by nonrenal routes of elimination which equals 40 mL/min in patients with no or mild heart failure



Digoxin clearance is proportional to creatinine clearance for patients with [*circles with solid line:* Cl = 1.303(CrCl) + 20] and without [*squares with dashed line:* Cl = 1.303(CrCl) + 40] moderate-severe (NYHA class III or IV) heart failure. Nonrenal clearance (denoted by the y-intercept) is lower for patients with moderate-severe heart failure because reduced cardiac output results in decreased liver blood flow and digoxin hepatic clearance.

INITIAL DOSAGE DETERMINATION METHODS

- The *pharmacokinetic dosing method* isthe most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. However, it is computationally intensive

- The *Jelliffe method* is similar to the pharmacokinetic dosing method, except a target total body store is selected based on specific disease states and conditions present in the patient. It is also computationally intensive. Nomograms that use the dosing concepts in the Jelliffe dosing method are available. The nomograms are for adults only, and separate versions are needed for intravenous injection, tablet , and capsule because of bioavailabilitydifferences among dosage forms. All three nomograms assume that digoxin total body stores of 10 μg/kg are adequate, so are limited to heart failure patients requiring this dose.

PHARMACOKINETIC DOSING METHOD

CLEARANCE ESTIMATE

Digoxin is predominately eliminated unchanged in the urine, and there is a good relationship between creatinine clearance and digoxin clearance

$$Cl = 1.303(CrCl) + Cl_{NR},$$

where Cl is the digoxin clearance in mL/min, CrCl is creatinine clearance in mL/min, and Cl_{NR} is digoxin nonrenal clearance.

A digoxin non renal clearance value of 40 mL/min is used for patients without heart failure or who have only mild signs and symptoms of heart failure. Patients with moderate or severe heart failure have significant decreases in cardiac output which leads to a reduction in liver blood flow and digoxin hepatic clearance. In these cases, digoxin nonrenal clearance is set to equal 20 mL/min in the equation

VOLUME OF DISTRIBUTION ESTIMATE

- The average volume of distribution for patients without disease states and conditions that change this parameter is 7 L/kg.
- Because obesity does not change digoxin volume of distribution, the weight factor used in this calculation is ideal body weight (IBW)
- For patients with renal dysfunction (creatinine clearance ≤30 mL/min), creatinine clearance should be used to provide an improved volume of distribution estimate (V in L) using the following formula:

$$V = \left(226 + \frac{298 * CrCl}{29.1 + CrCl}\right) \text{(Wt/70)}$$

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

a very simple pharmcokinetic equation that computes the average digoxin steady-state serum concentration (Css in ng/mL = μg/L) is widely used and allows maintenence dosage calculation:

$$Css = [F(D/\tau)] / Cl$$

$$Or \quad D/\tau = (Css \cdot Cl) / F$$

where F is the bioavailability fraction for the oral dosage form (F = 1 for intravenous digoxin), D is the digoxin dose in μg, τ is the dosage interval in days, and Cl is digoxin clearance in L/d.

The equation used to calculate loading dose (LD in μg) is based on a simple onecompartment model:

$$LD = (Css \cdot V) / F$$

where Css is the desired digoxin steady-state concentration in μg/L which is equivalent to ng/mL,V is the digoxin volume of distribution, and F is the bioavailability fraction for the oral dosage form

STEADY-STATE CONCENTRATION SELECTION

Digoxin steady-state concentrations are selected based on the cardiovascular disease being treated.

- For heart failure, steady-state serum concentrations of 0.5–1 ng/mL are usually effective. For initial dosing purposes, a target digoxin concentration equal to 0.8 ng/mL is reasonable.
- For patients with atrial fibrillation, steady-state serum concentrations of 0.8–1.5 ng/mL are usually needed to control the ventricular rate to 100 beats/min or less. An initial target digoxin concentration of 1.2 ng/mL is reasonable for patients with this disease state.

Example 1 MJ is a 50-year-old, 70-kg (5 ft 10 in) male with atrial fibrillation for less than 24 hours. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute an intravenous digoxin dose for this patient to control ventricular rate.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$CrClest = [(140 - age)BW] / (72 \cdot SCr) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$

$CrClest = 97\ mL/min$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient (ClNR = 40 mL/min since the patient does not have moderateto-severe heart failure):

$Cl = 1.303\ (CrCl) + ClNR = 1.303(97\ mL/min) + 40\ mL/min = 167\ mL/min$

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with atrial fibrillation, the desired digoxin concentration would be 0.8–1.5 ng/mL. A serum concentration equal to 1.2 ng/mL will be chosen for this patient, and intravenous digoxin will be used (F = 1). and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$D/\tau = (Css \cdot Cl) / F = (1.2\ \mu g/L \cdot 167\ mL/min \cdot 1440\ min/d) / (1 \cdot 1000\ mL/L) = 288\ \mu g/d$, round to 250 μg/d

Jelliffe Method

Because the goal of therapy is to provide the total body stores of digoxin that causes the appropriate inotropic or chronotropic effect, the maintenance dose (D in μg/d) is the amount of digoxin eliminated on a daily basis:

$$D = [TBS \cdot (\%lost/d)] / F,$$

where TBS is total body stores in μg/d, %lost/d is the percent of digoxin TBS lost per day, F is the bioavailability factor for the dosage form, and 100 is a conversion factor to convert the percentage to a fraction.

Combining the two equations produces the initial digoxin maintenance dose:

$$D = \{TBS \cdot [14\% + 0.20(CrCl)]\} / (F \cdot 100).$$

For patients with creatinine clearance values over 30 mL/min, digoxin total body stores of 8–12 μg/kg are usually required to cause inotropic effects while 13–15 μg/kg are generally needed to cause chronotropic effects. Since renal disease (creatinine clearance <30 mL/min) decreases digoxin volume of distribution, initial digoxin total body stores of 6–10 μg/kg are recommended for patients with poor renal function. If a loading dose is required, the total body store (TBS in μg) is calculated and used to compute the loading dose (LD in μg) after correction for dosage form bioavailability(F):

$$LD = TBS/ F$$

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1. *Estimate creatinine clearance.*

$CrCl_{est} = [(140 - age)BW]/ (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/ (72 \cdot 0.9\ mg/dL)$

$CrCl_{est} = 97\ mL/min$

2. *Estimate total body store (TBS) and maintenance dose(D).*

Digoxin total body stores of 13–15 μg/kg are effective in the treatment of atrial fibrillation. A digoxin dose of 14 μg/kg is chosen for this patient.

TBS = 14 μg/kg · 70 kg = 980 μg

D = {TBS · [14% + 0.20(CrCl)]} / (F · 100)

= {980 μg · [14% + 0.20(97 mL/min)]} / (1 · 100)

= 328 μg/d, round to 375 μg/d

3. *Use loading dose equation to compute digoxin loading dose (if needed).*

Digoxin total body store is used to calculate the loading dose after correcting for bioavailability:

LD = TBS/ F = 980 μg / 1 = 980 μg, round to 1000 μg